A Review on Adult Neurogenesis in Alzheimer's Disease

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy

Department of Pharmacy
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Declaration

It is hereby declared that

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2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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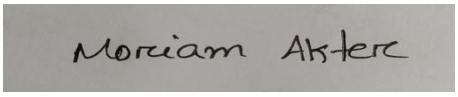

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Approval

The thesis titled “A Review on Adult Neurogenesis in Alzheimer’s Disease” submitted by Moriam Akter (16346042) of Summer 2016 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelors of Pharmacy.

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Ethics Statement

This study does not involve any human and animal trial.

Abstract:

In the adult brain, neurogenesis is the process through which neural stem cells mainly generate new neurons. Adult neurogenesis occurs in two regions of the CNS such as, the subventricular zone and the subgranular zone of the hippocampal dentate gyrus. Alzheimer's disease is an age-related, gradual and chronic neurodegenerative disease which can cause huge neuronal death and decrease cognitive function. Moreover, the patients with Alzheimer's disease mainly develop exceptional atrophy in entorhinal cortex in the process of adult hippocampal neurogenesis and the dentate gyrus constantly generating new granule neurons. There is a relation between AD and adult neurogenesis, and the differences in the field are also discussed here. In this review, I tried to present the therapeutic importance of promoting neurogenesis which is applicable to stop or treat cognitive deficiencies connected to neurodegenerative diseases and aging.

Keywords:

Neural Stem Cells, Neurogenesis, Hippocampus, Subventricular Zone, Dentate Gyrus, Progenitor Cells, Alzheimer's Disease.

Dedication

Dedicated to the Department of Pharmacy, Brac University.

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Table of Contents

List of Figures:

List of Tables:

Chapter 1

Introduction

Most neurons have generally been known to be terminally distinct in the central nervous system (CNS) and damaged neuron cannot be repaired (Ming and Song, 2011) .Due to limitations in study techniques that hindered neurogenesis-related studies in human being, it was a hot issue within neuroscientists (Ho *et al.*, 2013). In adult human brain the loss of neurons considered to be permanent, as damaged neurons could not be repaired (Eriksson *et al.*, 1998). During life, the mammalian can produce new neurons in brain (Braun and Jessberger, 2014). On the other hand, the long-standing theory indicate that neurogenesis reduces with the end of early postnatal development.

In the past few years of research study has showed that in neurogenesis process new neurons are produced in adults brain region. Neurogenesis might support everyone in enhancing treatments from Alzheimer's and epilepsy to stroke and traumatic brain injury for many conditions, illnesses, or harm as well as help everyone maintaining their sharp memories and thoughts, which are being seeking to activate and intensify by the researchers (Luzzati *et al.*, 2006).

1.1 Neuron

The neuron is the nervous tissue's structural organ, and neurons are the only components that execute nervous impulses in the nervous system. Three sections are composed of each nerve unit: the body, the fiber, and the terminal branches. Physiological conduction may take place from the body to the branches of the terminal as well as in the other direction. The dendrites and soma are receptive, that is, impulses from other neurons act on them, whereas the axon transmits impulses to its terminals that occur in the neuron, ('dynamic polarization' of the neuron) (Young, 1966). Other functions serve the other cell types, i.e. the different glial types, the ependyma, the

choroid plexus neuroepithelium, and connective tissue cells. It was found that in the nervous system, the classic neuron doctrine has been a central feature and has proven very useful as a working hypothesis (Golgi, 1906a).

1.2 Stem Cell

In all kind of mammalian species, including humans, neural stem cell can be found in both developing mammalian nervous system and adult nervous system. Neural stem cell is a cell which can generate or originate from neural tissue in the nervous system which has some potential for self-renewal. Through asymmetric cell division, cells other than themselves can be created (Palmer, Willhoite and Gage, 2000). Stem cell is limited in that, with the exception of the placenta's trophoblasts, like nervous system cells and this might generate any cell in the human body. Neural stem cells are unable to establish the organism's shape and function out of context (Thomson, 1998). Stem cells which located in nervous system are regenerating, productive cells including oligodendrocytes, neurons and astrocytes. In adult central nervous system, neural stem cells might generate (Taupin and Gage, 2002).

1.3 Neurogenesis

Adult neurogenesis is the phenomenon by which active and mature neuron cell is produced from nervous stem cell in the brain (Angevine, 1965). The whole process is beginning with blast cell division and produces mature and functional new neuron. Neurogenesis is usually a way of producing functional matured neuron from blast cells, and this process was occurred in developmental stages of mammalian central nervous system (Ramon y Cajal 1913). Researchers have recently found that newborn neurons are developed in different region of adult central nervous system (CNS). In most mammalian species, new neuron formation process (neurogenesis) occurs in subventricular zone (SVZ) and in the subgranular zone (SGZ).

Chapter 2

Alzheimer's Disease

Alzheimer's disease is the largest disorder of the 21st century. Moreover, it causes neuronal cell death by the deterioration of the nervous system's superior capabilities. For this, some significant cognitive changes occur such as learning and memory impairment, through systemic neurodegeneration in association with cortex and limbic system (Dickson, 1997). Neuropathology of AD is the neurofibrillary tangles development inside the neuron which primarily made of tau protein (Grundke-Iqbal et al., 1986). We can see that, in AD Tau protein is increased by hyperphosphorylation process which resulting a refusal reaction, in neuronal branching retraction. The development of senile plaques, most specific neuropathological characteristic of the disease, is another characteristic of AD (Morgan et al., 2004). They consist of a dense-looking extracellular substance, consisting primarily of b-amyloid peptide (Ab) which is formed by amyloid precursor protein (APP) proteolytic processing (Perl, 2010). Mutations in APP and presenilin 1 (PS1) (Schellenberg et al., 1992), (Goate et al., 1991) are caused by Familial AD (FAD) (Schellenberg et al., 1992), PS is a key player in the function of the c-secretase complex as a catalytic center. Amyloid precursor protein cleaves their peptide bond and increase amyloid-β (Aβ) peptides and it extreme mutation of APP can cause FAD (LaFerla et al., 2007). In Alzheimer's disease (AD) patient may initially loss memory and then gradually loss problem-solving, language and other thinking abilities. Usually, the patient with this condition become dependent on caregivers. In AD the nervous tissues are scatter and amyloid plaques are frequently encompassing by intracellular neurofibrillary knot and various cellular organelles. The white matter and synapses also follow these hallmark pathologies. The etiological

mechanisms that underlie AD's neuropathological changes remain unclear, but they are likely to be caused by both outside circumstances and hereditary (Reitz et al., 2011).

2.1 Alzheimer's Disease and Risk Factors

In Alzheimer disease dementia is common and it shows some symptoms like memory destruction, language and intelligence which are very important in our life. Dementia and AD are related to different risk factors. Of note, several known vascular risk factors for dementia are stroke or ischemic heart disease. It has been found that diabetes, hypertension, smoking, traumatic brain injury, psychological stress and obesity all raise the risk of dementia. However, AD remains unclear when cerebrovascular disease occur which affect the blood vessel and blood supply in the brain and it can be called vascular dementia, vascular changes in Aβ deposition have an etiological role (Marlatt and Lucassen, 2010). Alzheimer's disease is affecting the people whose age is more than 65 (Burns & Iliffe, 2009). Epidemiological studies have suggested that AD risk factors can be genetic and environmental. Genetic variants were repeatedly connected with membrane protein which attached with many tissues and neuron synapses and presenilin 1, 2 genes, family cases of AD and sporadic cases of AD were related with the Apolipoprotein (Apo) E4 genotype at late onset. Environmental factors can cause AD, like physical exercise, Mediterranean diet, and exposure to toxins (Chouliaras et al., 2010).

2.2 Pathophysiology of AD

Recently, pathophysiology of AD is primarily focused on neuropathological and genetic observations that point to the aberrant processing as core molecular events of APP and tau. However, most of the AD are caused by specific type of ApoE gene (Bird, 2005, 2008; Burns and Iliffe, 2009) which consistently shown to have a minimal impact on age (Bu, 2009; Lahiri et

al., 2004). AD may hamper the specific area of the brain which cause damage in neuron and synapses. In neurofibrillary tangles the neuritic plaques may form which mainly surround by Ab fibrils and tau protein (Dickson, 2001; Huang and Jiang, 2009). Plaques found outside a cell are formed by b- and g secretase from the endo proteolysis of the APP which increased development of Ab42 accumulation gradually of Ab42 and aggregation (Selkoe, 2001). Recent studies have found that amyloid degradation decreased because of progressive accumulation of Ab42. As, changes occur because of age in the microtubule-associated protein tau (MAPT) gene expression, hyperphosphorylation of tau protein can be formed by paired /straight filaments (can see in fig:1) (Mudher and Lovestone, 2002). The neurofibrillary tangles and ab fibrils cluster around the nervous tissue and it reduces the function of synapse and neuron. It is slowly damaged the cognitive function. In outstanding overviews, the pathophysiology of AD (Small and Duff, 2008) is identified by complex factors mainly involved in both APP and tau protein. The precise function of APP is not yet completely elucidated, despite many years of comprehensive research. The recent trends are regarding AD, extending the amyloid hypothesis. The over production of APP mainly cause acute reaction damage, such as vascular etiology damage (Hardy, 2009).

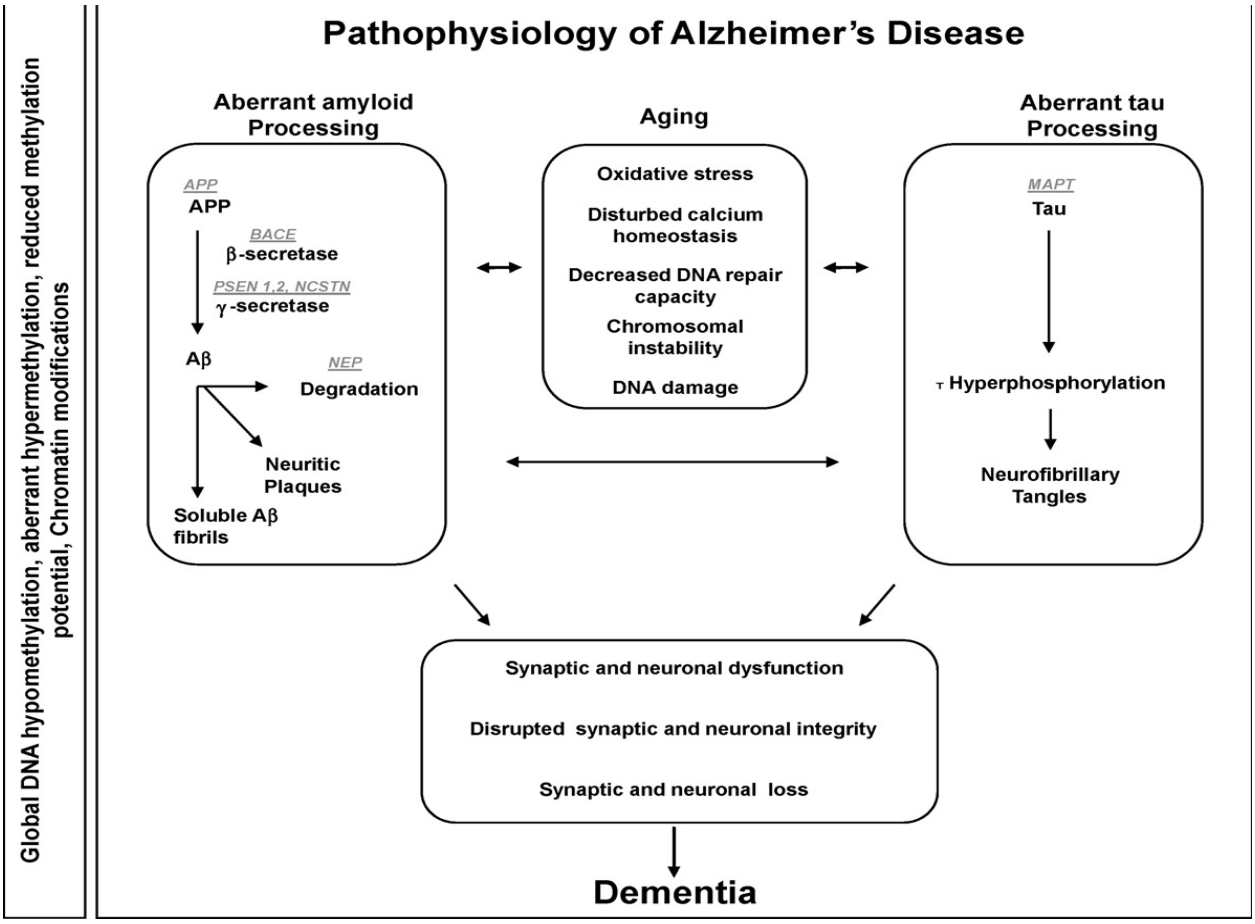

Figure 1: Schematic Summary of Potential Epigenetic Basis and AD Pathophysiology. AD's pathophysiology is dynamic interplay between aging factors, tau, and aberrant amyloid-precursor protein process in. Here, Amyloid Protein Precursor(APP), beta-Amyloid (Ab), Beta-site APP-Cleaving Enzyme 1 (BACE), Presenilin-1 (PS1), Presenilin-2 (PS2), Nicastrin (NCSTN), Neprilysin (NEP), tau-associated microtubule protein (MAPT). In italic form, genes are illustrated with evidence of epigenetic control of gene expression (Chouliaras *et al.*, 2010).

Chapter 3

Adult Neurogenesis

3.1 History

The first proof of adult brain neurogenesis by Joseph Altman arose from his studies in rats in the 1960s. Stem cells (NSCs) were first recorded by Altman and colleagues in adults. They reported the constitutive development of new neurons in both the hippocampal dentate gyrus and also the subventricular zone and olfactory bulb system (Altman & Das, 1965). The electrophysiological features of activated neurons joined with neighboring cells and inserted into internal neural systems were present in those newly developed neurons. The hypothesis that the brain tissue from a mammal is a post-mitotic device that does not generate new neurons has been reversed by these observations. Altman's experimental proof for rats, however, was not strong enough. At the time, the lack of neuron-specific immune cytochemical markers led to strictly morphological requirements being established. These constraints contributed to the extensive lack of acceptance of these findings (Altman & Das, 1965). The first direct proof of neurogenesis among adults in songbirds was published by Fernando Nottebohm in the 1980s. The entire concept of neuroscience has been modified by this study. It was claimed that the mature migratory birds has the capability of learning new songs through their new cells which were created by their brains and they develop new song memories with the help of such neurons. It opened up discussion about whether there was the same mechanism in humans. Weiss and Reynolds were the first to isolate and identify neural progenitors as well as somatic stem cells in test tube from the adult rodent brain. Over time, further experiments were carried out in various animal and the

consequences were helpful of continuing neurogenesis, as well as adult humans were reported for neurogenesis in 1998 (G. L. Ming & Song, 2005).

Researching markers and methodologies used to classify neurogenesis is a prerequisite for discussing published literature in this area. There are a variety of approaches and it only serves to introduce these ideas about the identification of NPCs depends critically on the right location, morphology of cells, and selective expression of proteins. Type-1 conventional glial cell and type-2 non-conventional glial cell co-expose unique

proteins that separate these cells within the DG SGZ, e.g. NPCs express Sox2 and Glial Fribrillary Acid Protein for Nestin (GFAP) (Lendahl et al., 1990) (Garcia et al., 2004). The special fundamental marker GFAP noticed in SVZ stem cells and subpial zones is also expressed in SGZ astrocytes (R.F. et al., 2005). The expression Sox2 describes the NPC pool with the ability to produce every three sensory position. Sox2 is part of the gene family Sox (SRY-related HMG box); this transcription factor is considered to be expressed during growth and binding in adult brain NSCs.

Amusingly, Sox genes also encode proteins that control transcription during growth and judge cell fate, e.g. the Sry gene encodes the element that specifies mammalian testis (sex-determining portion of the Y chromosome) (Koopman, 1999) (Avilion et al., 2003). The combined use of the birth date marker, Bromodeoxyuridine (BrdU), a synthetic thymidine analog usually injected in vivo, was analyzed with many of the protein markers mentioned above. During genome replication, BrdU is integrated into the DNA of dividing cells and allows for co-labeling with phenotypic molecular markers at a later level. The time between injection and euthanasia will critically evaluate the population of cells that has been created. Usually, data were measured: a) 3-6 weeks after injection to mark and label migration and living cells b) 24 hours after injection

to identify the population of proliferating cells. It is possible to identify and stereologically count proliferating and mature cells by using two animal cohorts with these survival periods. By co-labeling BrdU positive cells with additional markers, it can be established that the cell in question is actually a daughter cell of neural stem cells that has differentiated into a particular adult glial or neuronal phenotype. The double cell-fate studies allow the proper association of molecular markers with newly developed cells. The positioning of a BrdU positive cell also helps validate a mature cell phenotype. During formation, molecular markers for neurogenesis have been recognized and can be represented in other areas of the brain. For instance, previous rodent studies have shown that the Doublecortin (DCX) microtubule-related protein is generated in migrating, immature neurons that co-express class III tubulin-specific neurons (Tuj1) (Tuj1). Its distribution pattern contrasts with that of adult neurogenesis in, for instance, the amygdala. DCX is a very well molecular marker of neurogenesis in rodents; during cortical development in E14 mice, the DCXX function was discovered in utero electro permeabilization for appropriate movement to the neural tube of adolescent neurons (Bai et al., 2003). Radial migration is stopped when an RNAi is delivered against the 3'UTR of DCX, showing facts for non-cell-autonomous DCX speech elements. However, DCX is also present in cortical astrocytes and in separate neurodegenerative diseases in the adult cortex. To distinguish mature neurons and astrocytes very frequently in the field, markers such as NeuN (Mullen et al., 1992) and S100 are used. Since there is no evidence that these cells have been generated from endogenous stem cells, this suggests that DCX expressing cells could have additional functional roles in neurodegenerative conditions, such as glia-to-neuron penetration (R.W.H. et al., 2007). We will review observations on the separate neurogenesis process in the SGZ niche in the next section and further comment

on our capacity to detail mature neurogenesis classification and the probable of these special cells.

3.2 Plasticity and Regulation

Although neuronal permeability is thought to be the main neural shift leading to gradual improvements in cognitive activity, a recent and rare long-term structural plasticity is the attachment of new neurons to an existing circuit by adult neurogenesis. Approximately 9,000 new cells are estimated to be formed every day in the entire amygdala in young rats, but a large proportion of these cells die in some days (Cameron & Mckay, 2001). Even though number of new neurons implanted into the DG can be very limited, particularly during ageing, researchers see this continuing occurrence as a possibility for evolution. The principle of the Neurogenic Reserve notes that ongoing adult neurogenesis is a particular form of brain plasticity that facilitates behavioral adaptation that may influence the susceptibility to accumulating deleterious incidents (Kempermann, 2008). It is questionable that the clinical effects of adult neurogenesis will only become evident over long stretches of time by a global study of neurogenesis. The possibility that neurogenesis occurs over multiple organisms' lifespans suggests a significant role that is retained during evolution. Amusingly, the mechanism is particularly vulnerable to environmental/experience-dependent modulation, i.e. voluntary exercise and adaptation to the vivo fates of newborn cells for substantial contribution (Kronenberg et al., 2003). In addition, various studies have identified conditions that can regulate the growth and survival of maturing cholinergic neurons in adult rodents. Several control neurogenesis positively, such as estrogen (Saravia et al., 2004), environmental complexity (Brown et al., 2003), exercise (Kitamura et al., 2003) and NMDA-related excitatory feedback (Arvidsson et al., 2001), while others, such as stress (Pham et al., 2003), cholinergic denervation and aging (Kempermann et al., 2002),

decrease neurogenesis levels. Head injury, epileptic seizures (Holmes, 2004) and intermittent global and focal ischemia (Yagita et al., 2001) increase hippocampal neurogenesis, but there is insufficient understanding of the effects on the properties of hippocampal circuits and Alzheimer's disease (Castellani et al., 2008). While its connections between Alzheimer's disease and neurogenesis seem controversial, associations among neurogenesis and depression have been established. Depression and antidepressant drug activity have been suggested by stress-induced reductions in neurogenesis (Lemaire et al., 2000). Both the mineral corticoid (MR) and glucocorticoid (GR) receptors are expressed by adult CA1 pyramidal and DG granular neurons. Long - term stress exposure can cause changes in HPA input that may contribute to over-exposure to glucocorticoids. On note, a major risk factor for Alzheimer's disease is elevated blood levels of stress hormones (De Kloet et al., 2005). It is also an enigma when neurogenesis arising during these pathological disorders leads to functional recovery; there are no well define differences between the capacity for recovery and those causes responsible for functional recovery.

3.3 Behavior

Notably, not only can the aforementioned factors affect neurogenesis, but they also associate with behavioral function changes, including hippocampal learning and memory (Drapeau et al., 2003). This indicates that neurogenesis and cognitive function have a direct relationship, in an enriched housing climate, for instance, housing rodents (Kempermann et al., 2002) or giving them contact to a running wheel (Kitamura et al., 2003) enhances the endurance of progenitor cells and also helps to increase the efficiency of the water maze mission. On the other hand, other factors such as stress result in a reduction in neurogenesis impact behavioral performance on such tasks (an inducible genetic modification system was used to immobilize adult-born

hippocampal neurons through Bax expression in hippocampal neural activators in one of the most direct studies to answer this issue. At the same time as less complex types of spatial memory were unchanged, these types of spatial memory were unchanged (Dupret et al., 2008). Previous research has shown that spatial learning facilitates the death of newborn neurons in DG (Shors, 2003). Neurogenesis also tends to be included in the control of behavioral success and more complex facets of hippocampal learning and memory, at least partly. Highly accurate measurement of hippocampal-dependent activities and improvements in synaptic function has also measured the function of neurogenesis. Researchers observed in adult rats that the reinforcement of hippocampal-dependent residue was specifically interrupted by a substantial decrease in the number of newly produced neurons, a task in which the animal must be correlated with inputs separated in time. This reduction in neurons in hippocampal-independent activities had no effect on academic achievement (Shors et al., 2001). Subsequent research has also shown that in new memories, adult neurogenesis plays a part in encoding time (Aimone et al., 2006). Neurogenesis thus tends to be involved in the regulation of particular hippocampal areas of visual output and, as such, may be essential in congenital specific impairment-related diseases such as AD in this field. Synaptic number changes have important functional consequences on behavior, particularly perception. Synaptophysin modifications are more concerned with disease development than plaque loading or cell death in neurodegenerative diseases (Terry et al., 1991). During natural ageing, changes in synaptic density have been demonstrated; there is an inverse association between age and presynaptic terminals. Hippocampal synaptogenesis pathways and their direct importance for learning and memory are now being identified (Dupret et al., 2007). Owing to a lack of activity correlated with synapse power, hippocampal behavior can be further influenced by decreased neurogenesis. Ongoing

adult neurogenesis indicates a contribution to the enhancement of synaptic density as new receptors are formed. Recently produced cells also have lower long-term potential levels, so adjustments in their numbers can affect the hippocampal circuit's functioning. Adult neurogenesis maintenance may stabilize synaptic density, alleviate synapse depletion and decrease age-related changes. It has been shown that hematopoietic stem cell loss results in premature aging (Ito et al., 2004), but no information on the relationship between stem cell loss and actual human neurological dysfunction has been collected at present.

3.4 Behavior and Environment

Mechanisms are not well understood in the dentate gyrus of the adult amygdala by which new neurons are formed. Latest studies in mice suggest that exposure to an enriched atmosphere (Greater environment, varying stimulation and greater potential to promote social interaction, physical exercise and education) (Rosenzweig et al., 1962). The result was a large improvement in neurogenesis over control conditions (Kempermann et al., 1997). Self-imposed activity on a spinning wheel reinforces neurogenesis, equivalent to enrichment. Moreover, in the DG of the mouse, running increases cell production (Van Praag et al., 1999). Besides these environmental and behavioral manipulations, the amount of granule cells is increased by many pathological events: seizure damage to the hippocampus (Parent et al., 1997) (Bengzon et al., 1997), ischemia (Liu et al., 1998), and mechanical lesions (Gould & Tanapat, 1997). Glucocorticoid hormone stress or elevated levels inhibit growth action in dentate gyrus (Cameron et al., 1995) (Gould et al., 1992) (McEwen, 1996). Administration of elevated corticosterone levels, for example, reduces cell division in the grown-up rat hippocampus.

3.5 Researches on Humans

Along with his colleagues, Maurice Curtis studied the brains of dead cancer patients who had recently been administered with bromo-deoxyuridine (BrdU), a newly synthesized DNA-integrated chemical used by oncologists to surprise them with the imaging and monitoring of tumor growth, and originate BrdU-positive cells in the brain of the rhinencephalon of patients. Curtis' colleagues had used antibody discoloration to demonstrate that when traveling through the rostral migratory medium, the neuroblasts began to separate into olfactory bulb. The cells started to divide, becoming adult olfactory neurons, until they reached the bulb. The results indicate that neurogenesis can occur during human life, because cancer patients whose brains have been observed are between the ages of 38-70 years. The role of these newly formed cells is unclear, although in old age, they could be involved in sensing and recalling new smells (Taupin, 2005). Once more, it is proposed that stem cells not only travel to the olfactory bulb, but also skip the RMS and pass to the cerebral cortex and basal ganglia. This is important because portions of the basal ganglia deteriorate in motion conditions such as Parkinson's disease and in Alzheimer's disease, specific cortical parts degenerate. The prospect of stem cells from the RMS entering these regions may also provide a way to establish novel neurodegeneration therapies (Costanzo, 2000).

3.6 Function of Adult Neurogenesis

Adult NSCs and spontaneous neurogenesis give great promise for the management of brain disorders (Kim et al., 2012). Similar to adult stem cells working with certain tissues and organs, NSCs are expected to contribute to tissue regeneration and dead cell replication after brain injury (Collin et al., 2005). In learning and memory, new neurons are decisive. An enticing and testable theory is that newly generated neurons in the adult CNS display specific physiological properties

at particular stages during their maturation process, allowing them to function as significant intermediaries for constructional flexibility. In turn, this active constructional flexibility is essential for affective memory and learning and maybe for mood (hopelessness). Latest studies have also shown that new neurons have distinct defensive and offensive properties in comparison with mature neurons. Neural synapses also have a surprising ability to migrate and disperse axons and dendrites in an aggressive environment that is generally capable of inhibiting to mature neurons (Kempermann et al., 2004). Instead of immediate gains, the possible effects of adult neurogenesis to memory are more likely to appear in long-term modifications.

3.7 Perspective

The decline of an ancient belief and the emergence of another innovative extent of adult neurogenesis have been experienced in the last decade. Now, from recording the nature of adult neurogenesis in order to understand its control processes and roles, the emphasis of the newly developed field has changed. From wide fascinating and unusual features of adult neurogenesis is that in the mature CNS, an area quite distinctive from the embryonic CNS, where neural growth has historically been observed, the entire neuronal growth mechanism is reinterpreted. In addition to showing the remarkable proliferative capacity of the mature CNS, the display of successful neurogenesis in adult humans often increases hopes that the injured adult CNS will rebound following damage or congenital psychiatric conditions. Identifying the fundamental pathways under regular and abnormal circumstances that control adult neurogenesis will provide the foundation for transplant recipients using either embryonic adult neural stem cells or implanted cells from various sources. The area of adult neurogenesis is, as history indicates, powered by technical advancements. The best is yet to come, backed by innovative techniques of live visualization, standard retrovirus genetics, new animal studies, and cognitive stimulation.

3.8 Clinical Implications

The evidence of the fact that neurogenesis exists in the mammalian adult central nervous system (CNS) in the brain tissue and neural stem cells (NSCs) is of immense significance to our comprehension of nervous system pathophysiology. This suggests that adult neurogenesis, especially during neurotoxicity, contributes to the pathogenesis of behavioral diseases and conditions (Imayoshi et al., 2009). Numerous studies have shown that neurogenesis can affect hypothyroid animals, evaluate anxiety and stress, control spinal cord compression, memory and concentration, and promise to heal other neurological diseases such as Parkinson's disease, Huntington's disease and Alzheimer's disease (Berhe, 2015).

3.9 Mechanism of Neurogenesis

Adult mammalian brain neurogenesis happens throughout life and has been specifically illustrated under natural circumstances at 2 sites: the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the hippocampal dentate gyrus (Zhao et al., 2008).

3.9.1 Subgranular Zone of Hippocampus

It is at the origin of the granular cell layer of the hippocampus between the hilus and the dentate gyrus, subconsciously on the inside of the hippocampal parenchyma (Figure 1) (Imayoshi et al., 2009). This entails a synaptic prototype extracellular matrix in the DG that during adulthood produces significant amounts of new particle size neurons (Deng et al., 2010).

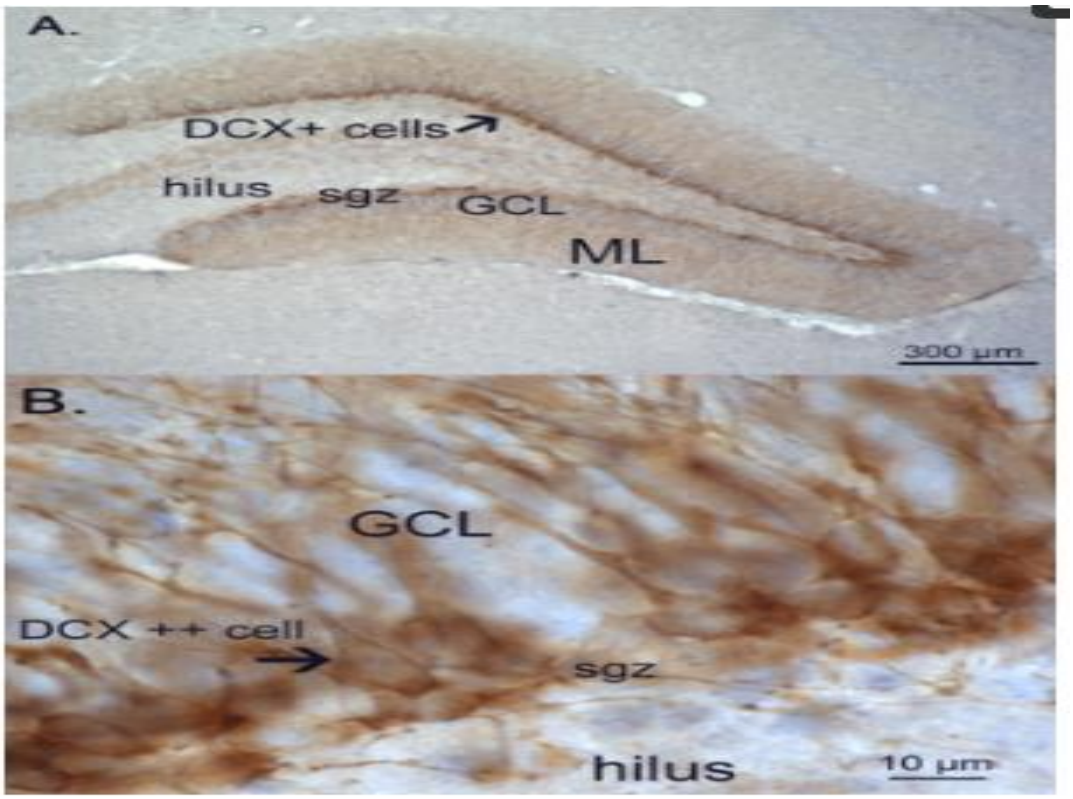

Figure 2: Photomicrograph of SGZ Neurogenesis Inside Rat Brain: a) dentate gyrus regions: hilus, sub-granular zone (SGZ), granule cell layer (GCL) and molecular layer (ML); double cortin (DCX) stained cells; b) Nearer view of SGZ between GC and Hilus. Infant cells continue to develop and transfer their dendrites through the moss - covered fiber duct through the hilus and other formations inside the hippocampus through the molecular layer and their cell types. (Jacobs et al., 2000). (Oomen et al., 2009). In the SGZ, two kinds of neural progenitors may be defined. They are: hippocampal progenitors of type 1 and type 2 (Hodge et al., 2008).

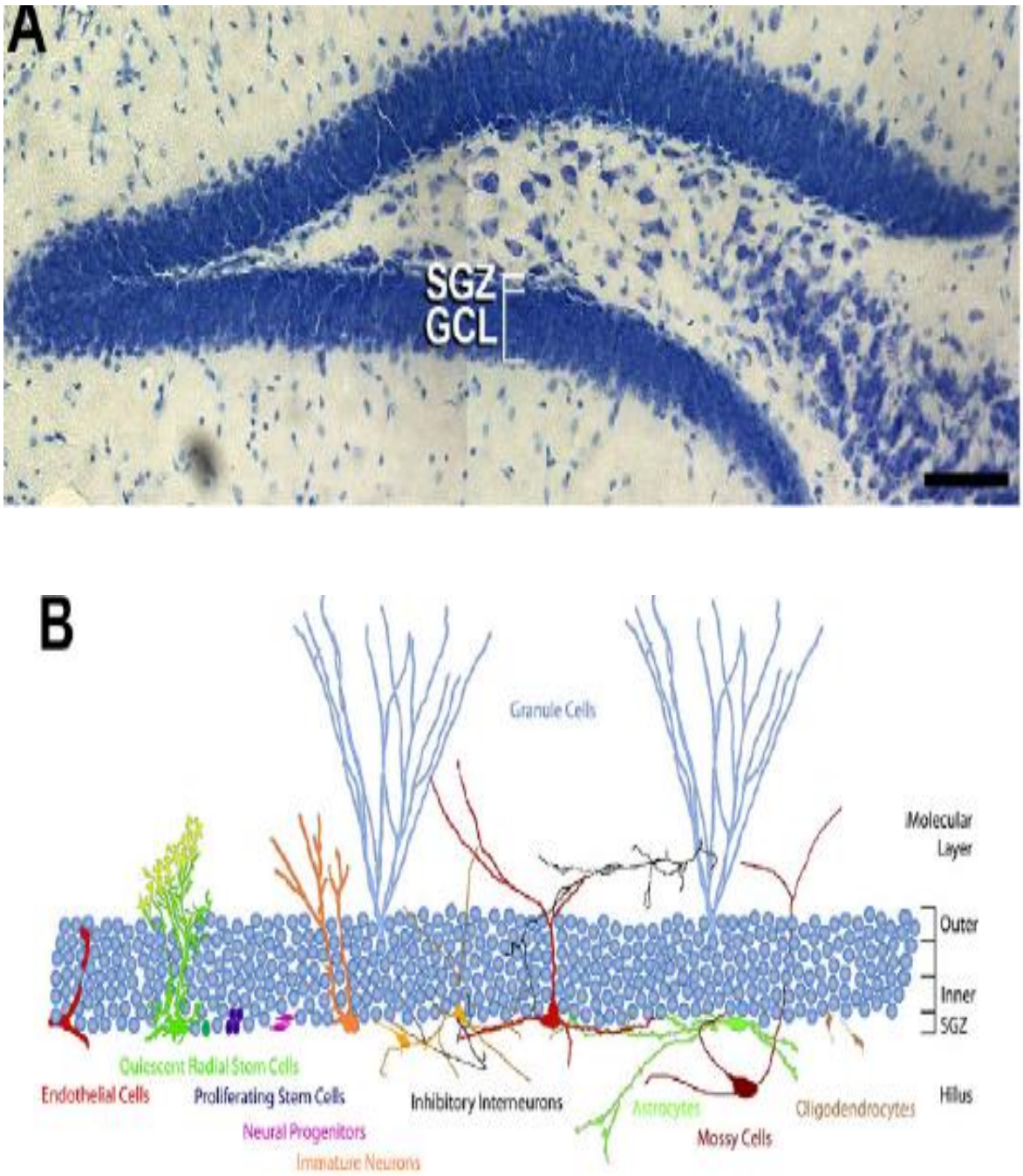

Figure 3: Recognition in The Adult Mouse SGZ of Neurogenic Niche Genes. (a) Thionin-stained, subgranular zone (SGZ) DG mouse cryosection found at the base of the granule cell layer (GCL) and adjacent to but distinct from the hilus. (b) Schematic illustration in the SGZ of the many different types of cells identified. Also seen are excitatory mossy cells in the hilus and mature granule cells. The corresponding labels share the same color as the type of cell (Jessberger et al., 2008).

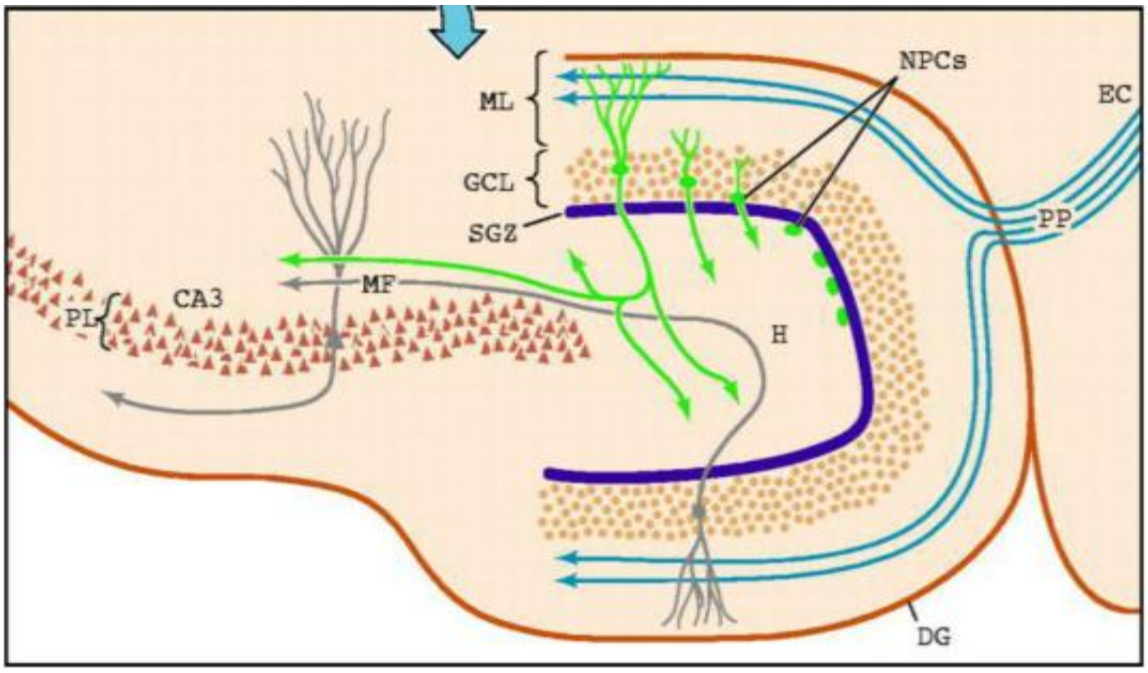

Figure 4: SGZ Neurogenesis Where in The Peak A Transverse Portion of The Development of The Rodent Hippocampal Showing The Main Divisions of Cytoarchitecture. DG indicates dentate gyrus, EC indicates entorhinal cortex S indicates subiculum. Neurons progenitor cells (NPCs) propagate at the rim divide into neurons and conceptually pass to the porous membrane through the GCL (ML). Cell bodies stay at the GCL, project through both the ML dendrites, and project into the hilus and CA3 axons. New (green) shown neurons; mature gray shown neurons; MF, mossy fibers; PL, pyramidal layer (Jacobs et al., 2000).

The interesting finding is that isolating cells are clustered in dense vasculature-associated clusters and that approximately 37% of all dividing cells are immunoreceptor to endothelial markers (Palmer et al., 2000). Approximately 25% of newly developed neuroblasts will continue to exist and grow to turn out to be DG grain neurons (Kempermann et al., 2003). These newly hatched neurons may play a role in existing processing information and facilitate the functional differentiation of conceptual memories (Akers et al., 2014). Subventricular lateral ventricle zone the subventricular zone (SVZ) is a harmonizing brain formation located in the lateral ventricle walls. It constitutes the largest group of proliferating cells and is dominated by neurogenesis-influencing heterogeneous stem and progenitor cell populations.

3.9.2: Subventricular Zone of Lateral Ventricle

The subventricular region is a combined brain network situated around the posterior wall of the lateral ventricles. It comprises the largest proliferating cell population and is populated by heterogeneous populations of stem and progenitor cells (Alvarez-Buylla & Lim, 2004). Unlike SGZ neuroblasts that transfer a small distance to the neighboring granular cell layer, SVZ neuroblasts move to the olfactory bulb through the rostral migratory stream (RMS), where they differentiate between sensory neurons (Akers *et al.*, 2014)(Fig. 3).

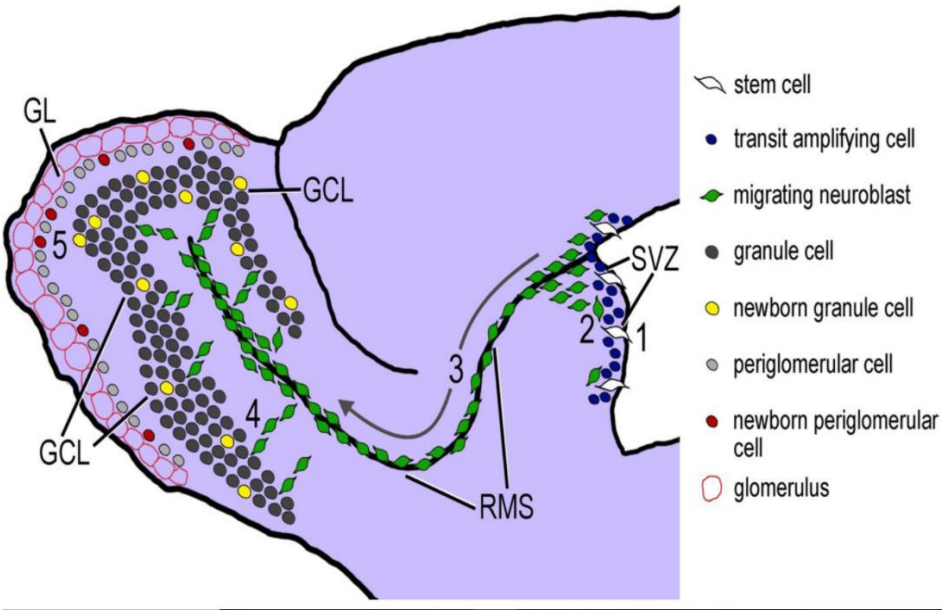

Figure 5: Representation of The Neurogenesis of The Adult Mouse Brain in Adult SVZ and OB. 1) Adult-born olfactory precursors primarily proliferate within the SVZZ 2) then distinguish into neuroblasts 3) After that neuroblasts migrate indirectly along with the RMS to the main OB 4) adult-born neuroblasts radially migrate to the OB 5) Aadult-born cells in the OB grow to form the granular, peri-glomerular and external plexiform cell layers of local interneurons. GCL, granular layer of cells; RMS, migratory rostral stream; GL, glomerular layer (G. L. Ming & Song, 2005) (Abrous et al., 2005) (Sui et al., 2012).

Chapter 4

Neurogenesis in Alzheimer's Disease

The main objective in this field, considering the significance of animal AD models, trying to evaluate the process of neurogenesis in AD. Therefore, the found result of patient detection was not solved, and it may be effect of irregular method run by different laboratories (Table 1). Braak and Braak (1991) operated a research and they collected individual part of nervous tissues which are developing different stages of AD. They differentiate the phase into two phases, the first group is about classification of Ab maturation and another for changes in the neurofibrillary. Phase A indicated the deposition of isocortex in bottom part, Phase B indicated the hippocampal formation where ab protein found by isocortical activity. Then, phase C suggested that ab is found in all isocortex area. In a nutshell, phases I and II, transentorrhinal region present; phases III and IV, limbic field presence; and phases V and VI, isocortical region mass presence (Braak and Braak, 1991a) .

Table 1: Discrepancies in Adult Neurogenesis Observation Taken from Different Strategies and Models (Varela-Nallar et al., 2010).

Model	Mutation	Results	Author
AD patients			
Human	nd	Increased proliferation in hippocampus, measured by KI67 marker	Nagy et al. (1997)
	nd	Increased proliferation; the differentiation was reported to be mostly to neuron.	Jin et al. (2004b)
	nd	Reduced proliferation rate in SVZ	Ziabreva et al. (2006)
	nd	High proliferation, but mostly differentiated in glia in presenile AD	Boekhoorn et al. (2006)
Animal model			
Single mutations			
PS1	PS1 P117L mice	Neural progenitor proliferation was unaffected, but new cells are unable to survive.	Wen et al. (2004)
	PS1 A246E mice	Increased proliferation, but low rate of survival in new cells	Chevallier et al (2005)
	PS1 M146V	Reduced NG in the dentate gyrus in tg mice	Wang et al. (2004)
APP	PDAPP mice	Age-dependant decrease in SGZ proliferation in tg mice	Donovan et al. (2006)
	PDGF-$APP_{Swe,Ind}$	Increased proliferation and neuronal commitment in tg mice	Jin et al. (2004a)
Double mutations	APPswe/PS1ΔE9 mice	Reduced proliferating cells in tg mice, and this can be rescued with enriched environment	Hu et al. (2010)
	$APP_{2576}/PS1_{M146L}$	Increased survival in adult-generated neurons after Aβ immunotherapy	Biscaro et al. (2009)
	APPswe/PS1ΔE9 mice	AD-degree dependant decreased NG in tg mice, no gender difference	Taniuchi et al. (2007)
	$APP_{K670N/M671N}/PS1_{M146L}$	Increased proliferation, but the differentiation ratio in glia and neurons was similar in tg mice	Yu et al. (2009)
	APP-PS1; PS1;APP	Diminished NG in double knock-in tg, no effects on each mutation alone	Zhang et al. (2007)
Triple mutations	$APP_{Swe}/PS1_{M146V}/tau_{301L}$	Impaired ability to generate new neurons, and this increases with age	Rodriguez et al. (2008)

AD, Alzheimer's disease; NG, adult neurogenesis; tg, transgenic.

Therefore, in order to eventually address the question whether neurogenesis in human patients is elevated or decreased, it would be appropriate, as a technical standardization and assess neurogenesis shall apply the various Braak stages of the disease. As an example, neural progenitor proliferation in presenile AD brains was studied (Boekhoorn et al., 2006) and it showed neural multiplication improvement but lowered neurogenesis in hippocampus because this multiplication changed the gliogenesis and vasculature (Boekhoorn et al., 2006). It is found in comparable research based on the neurogenesis of SVZ (Ziabreva, Perry, et al., 2006). In this

research, a substantial decrease of NSC proliferation relative to age-matched controls in AD patients.

From (Ziabreva et al., 2006) increased proliferation but poor survival rates for new neurons have also been suggested in patients with AD (Shruster et al., 2010), based on human and animal AD template, that is currently the most accepted theory. However, the cell cycle irregularity might lead to degeneration of the new neuron (Bonda et al., 2010). Adult new neuron formation mainly follow some pathways, the molecular neuropathology of AD has also been established. In AD pathology, AD is decreased when APP cleavage occur and a-secretases release SAPP and EGF-modulated neural multiplication in SVZ (Caille et al., 2004). The decremental neurogenesis also occur in limbic areas of hippocampus brain region and it causes FGF-2 apoptosis in patients with AD. A strong mitogenic factor (FGF-2) can promote neural proliferation and also can keep neural precursors infantile (Johe et al., 1996). FGF-2 factor mainly do tau protein phosphorylation and proclamation and this mechanism is run by glycogen synthase kinase-3b (Tatebayashi et al., 1999). Mitogenic factor (FGF-2) inhibits adult neurogenesis by recapture trophic factors for example ciliary neurotrophic factor and glial-derived neurotrophic factor (Chen et al., 2007). Current research examines whether neurogenesis in patients with AD is upregulated in brain SVZ part in contrast of age-matched controls and they run a test which shows connection between the neurogenesis and neurochemical substrates.

4.1 Discussion:

In Musashi immunoreactivity, a remarkable ninefold reduction was noticed in SVZ region of AD patients against age-matched controls, and it indicated the reduction of similar neural progenitors. In specific report, reverse connection was found between Musashi's

immunoreactivity in the SVZ and ChAT in the temporal cortex, so it suggesting a connection in both conserve cholinergic function and preserved new neuron formation. In rodent studies, the found result indicated that Meynert nucleus basalis lesions were linked with significant reduction of neuronal parent cell in 2 vital neurogenic regions (Cooper-Kuhn, Winkler and Kuhn, 2004). Braak staging, CERAD, ChAT activity and modest non-significant associations were revealed the extent of pathology between plaque and tangle. It was also indicated that the cholinergic deficiency and pathological characteristic of AD might have antagonistic behavior on multiplication of uniform parent neuronal cell. In the SVZ the nest immunoreactivity was hard to recognize. The expansion of GFAP immunoreactivity in AD patients relative to controls were not found and it indicated that nestin-labeled stem cells were not astrocytes cell instead it showed some similar characteristics. Whenever disappear, it may cause an expansion of progenitor activity by differentiation process which also develop the mass number of unused progenitor cells at intermediate stages. Moreover, it may not be feasible to cut confounding effects of nestin binding (nonspecific) with other cells. It is hard to reconcile the current results (Jin et al., 2004) which featuring the progenitor activity proliferation in the SGZ region. Neurogenesis processes were began in the two different progenitor regions of AD and in the SGZ region more plaque and tangle pathology were contemplated. Therefore, it might be necessary to recreate jin's work. To do so, the work shall be conducted in an independent group along with a better age-matched control group. This will ensure about the results which were not briefly explained by several factors such as differences between ages. This phenomenon will establish better understanding and relationship between the severity of the disease & neurogenesis. The results indicate a number of potential therapeutic possibilities. It would be important, for example, to decide if neurogenesis is impaired by cholinergic treatment or

anticholinergic drugs. In addition, the findings show that in different stages and phase of AD the amount of neural stem cell reduces. There are strong sources of potential therapeutic benefits, as neurogenesis in animal models has been shown to enhance a number of medications, including statins.

However, it was found that Musashi1 participate to increase the neural stem cell which help the c ell to long durability and multiplication (Imai et al., 2001).

Chapter 5

Drug Used to Treat Alzheimer's Disease by Enhancing Adult Neurogenesis:

5.1 Donepezil:

Donepezil is a selective and potent inhibitor of acetylcholinesterase (AChE). In cholinergic dysfunction donepezil is used to treat Alzheimer's disease (Ogura et al., 2000). Here, the dysfunction of medial septal nucleus which contain huge number of cholinergic neurons in the adult hippocampal dentate gyrus (DG) in rats has recently been stated to suppress neurogenesis (Whitehouse et al., 1982). Then in normal rats, it decided whether donepezil that triggered the brain-cholinergic system (receptor which is stimulated by acetylcholine) and it modulated neurogenesis in the dentate gyrus of the hippocampus. It was treated orally with donepezil which is given 0.5 or 2 mg/kg once a day for four weeks. In parallel with 5-bromo-2-deoxyuridine (BrdU) injection to mark the cells that are dividing. In order to cause cholinergic activity in rats, the doses of donepezil that were used in this research were recorded. The animals were sacrificed one day after the end of drug therapy, and immunohistochemical analysis was conducted. After applying Donepezil it increased the amount of 5-bromo-2'-deoxyuridine (BrdU)-positive cells in dentate gyrus. Drug had no effect on the quantity of BrdU (5-bromo-2'-deoxyuridine) -positive cells that have been tested for the neuronal marker NeuN (neuronal nuclear protein) as well, or not even on the proportion of positive nuclear antigen growing cells in dentate gyrus. Such reaction suggested that donepezil bolster new neurons in the DG without influencing neural progenitor cell proliferation. These findings indicate that, donepezil facilitates central transmission of cholinergic drugs and via CREB signaling increases the existence in the DG of newborn neurons (Kotani et al., 2008).

5.2 Ethosuximide:

Ethosuximide (ETH) is an Anti-epileptic drug (AED) which is widely used in seizure absence. ETH slows age-related changes and indicates that neurodegenerative disorders and age-related diseases may be a possible therapeutic candidate (Collins et al., 2008). The study of the influence of ETH on the replication and neuronal differentiation of rat multipotent NSC and amyloid beta (Aβ) toxin adult hippocampal neurogenesis induced AD like phenotypes in rat models. Here, ETH highly mediated neural stem cells (NSCs) which can proliferate and differentiate into neurons in the nervous system. In rat AD model, ETH improved proliferation of NSC and differentiation of neurons, and decreased toxicity and neurodegeneration regulated by Aβ toxin, Owing to behavioral therapy. ETH slows age-related changes and indicates that neurodegenerative disorders and age-related diseases may be a possible therapeutic candidate (Collins et al., 2008). The study of the influence of ETH on the propagation and neuronal development of rat multipotent NSC and amyloid beta (Aβ) toxin in adult hippocampal neurogenesis induced AD like phenotypes in rat models. In vitro the hippocampal related NSC, ETH potently mediated NSC neuronal differentiation and multiplication. In rat AD model, ETH increased NSC Neuronal differentiation and multiplication and decreased toxicity and neurodegeneration induced by Aβ toxin, leading to behavioral recovery. ETH has been inhibited by amyloid beta (Aβ) which is neurotoxic and suppressed the neurogenic process. On the other hand, AktWnt/β-catenin mainly helps in cell growth/proliferation and activate gene expression in the hippocampus region of adult brain. ETH are triggered the Wnt/β-catenin and PI3K/Akt transduction pathways and believed to be associated in cell proliferation by inhibiting cell apoptosis. The mitogenic and neurogenic impact of ETH were effectively blocked by suppression of PI3K/Akt and Wnt/β-catenin pathways. Studies on docking in silico molecular

target for casting indicate that Ethosuximide reacted with GSK-3β, Dkk-1, Akt and induces cell proliferation. In vitro neural stem cell can cause cell multiplication and development in adult hippocampus region which occur by signaling PI3K/Akt pathway and Wnt/β-cateninin and is indicated by ETH. ETH induces in vitro neuronal variation and multiplication of NSCs which is collected from rat hippocampus region. It stimulates the formation of new neuron in hippocampus region of adult rats brain, also modifies the NSCs deficiency. Moreover, the rat model (Aβ) which has AD are characterizing learning and memory deficits ('Ethosuximide enhances neurogenesis', 2015).

5.3 Valproic Acid:

The frequently used mood stabilizer (decrease abnormal activity in brain) antiepileptic (control seizures) drug name is valproic acid (VPA), it has the potential effect that regenerate nervous cells (neuroprotection) and its applicable for AD. In addition, VPA might stimulate both in vitro and in vivo new neuron formation process (neurogenesis) of neural progenitor and stem cells through numerous signaling pathways. Via multiple mechanisms, VPA exerts many possible maintenance of neuronal structure (neuroprotective) in AD. It is mainly inhibiting glycogen synthase kinase3 (GSK-3) and targeting through different zone on AD pathogenesis. The cell death (attenuating excitotoxicity) caused by glutamate and VPA mainly decrease apoptosis and promoting neuronal survival. Researchers have found that, VPA exerts synergistic effects in glutamate-related nerve cell death (neurodegenerative) diseases treatment for example, AD along with GSK-3 blockers. VPA has been found to induce neuronal differentiation as an HDAC inhibitor, it terminate glial differentiation and activate neural progenitors in adult hippocampal brain region by modulating the NeuroD gene which is unique to neurons (Hsieh *et al.*, 2004). Liu et al. indicated that promoting the development of functional neurons or astrocytes by

inhibiting HDAC, VPA could restrict the differentiation of oligodendrocyte progenitors towards oligodendrocytes. Evidence strongly suggests that, HDAC inhibitors is mainly increased the histone acetylation and ease the sprouting of dendrites. Also, HDAC inhibitors indicate the development of neural network, learning and memory in adult brain. For this reason, VPA is an appropriate therapeutic agent in AD which is a neurodegenerative diseases (Fischer *et al.*, 2007). After providing VPA in therapeutic concentrations it shows numerous neuroprotective and neurogenesis actions. It is helpful in AD treatment and has a greater penetration effect in central nervous system (Zhang, Li and Zhang, 2010).

5.4 Levetiracetam

Levetiracetam chemical name is S-alpha-ethyl-2-oxo-pyrrolidine acetamide. It is a second-generation antiepileptic medicine and works in different type of seizures. LEV can modulate calcium penetration throughout the cell and it works by blocking N-type channels. LEV decreases potassium penetration throughout the cell and cellular damage by regulating membrane depolarization (Niespodziany et al., 2001). Different studies have shown that by inhibiting lipid peroxidation, neurons are defended by LEV from toxicity caused by kainic acid (Oliveira et al., 2007). In addition, by decreasing lipid peroxidation and the production of nitric oxide in hippocampus, LEV can counteract oxidative stress (Ueda et al., 2009). Some researcher have concentrated on the effect and associated mechanisms of LEV on hippocampal new neuron formation. Therefore, the cell proliferation and neuronal segregation of systemic delivery LEV in hippocampal DG were investigated in the present study using Ki-67 (a cell proliferation marker) and double cortin (a neuroblast marker, DCX). In the adult mice brain of DG region , LEV effects on neurogenesis and their pathways were also studied (Yan *et al.*, 2018).

Chapter 6

Conclusion:

In this review it is found that adult hippocampal neurogenesis is a highly modulated physiological process through which newborn neurons are united in preexisting circuits. The anatomy, integration and plasticity of these new neurons in the brain have been studied by various perspective. Behavioral tests proclaimed that adult neurogenesis plays a crucial role in some hippocampal functions. It also affects the plasticity of the hippocampus which can gain new memories. This is an important part of adult neurogenesis in SGZ. Hippocampal neurogenesis is decreasing because of aging. Moreover, different type of factors is working here to reduce the neurogenesis which is related to age. Researchers have found that different growth factors and hormones could restore in old mice in order to generate the number of neurogenesis. It is suggested that the basic components of neurogenesis are sustained throughout the life and it increases the probability that regulating the neurogenesis process that prevent the cognitive deficit which is related to neurogenesis loss. This research mainly showed us opportunity for the treatment of neurodegenerative diseases, such as AD which is caused due to neuronal loss also neurogenesis is diminished here.

Also, there has been some argument regarding AD which mainly caused the proliferation of neural precursors cell. On the other hand, newborn neurons may not be able to mature and fully merged in the hippocampal circuitry at this point. Future studies should focus on different type of stimuli and factors which might enhance the development, incorporation and the function of newborn neurons under some pathological conditions. This review will help to explain the therapeutic importance of promoting neurogenesis which is applicable to stop or treat cognitive deficiencies connected to neurodegenerative diseases and aging.

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