REVIEW ARTICLE

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Adult Neurogenesis: Facts and Potential Targets in Some Neurological and Neurodegenerative Diseases

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ABSTRACT

Adult neurogenesis is a process where new neurons are generated post-natally from neural stem cells maintained till adulthood. These neural stem cells are maintained in the hippocampus and the olfactory bulb although recent evidence has established their presence in other regions of the brain. Adult neurogenesis was first thought to be impossible due to several factors, one of which includes the integration of these newly formed neurons into the already existing neuronal circuitry in the brain. However, the development of new immunohistochemical techniques specific for neuronal and neural stem cells and confocal imaging have improved the evidence of neurogenesis since its discovery in the 1960s. Adult neurogenesis has been implicated in brain functions and its alteration is associated with various neurodegenerative diseases. Manipulations of adult neurogenesis and the several factors affecting it can be used to better understand and treat neurological and neurodegenerative conditions. This review discusses a general overview of adult neurogenesis, the factors affecting it and some neurological and neurodegenerative diseases relating to alterations in neurogenesis.

Key words: *Neurogenesis, Hippocampus, Neural stems cells, Olfactory bulb, Neurodegenerative diseases*

INTRODUCTION

Neurogenesis is defined as a process of generating new neurons, both inhibitory and excitatory from neural stem cells (NSCs) or progenitor cells (Jin 2016). It can simply be referred to as the birth of new neurons. It occurs during embryogenesis and is responsible for the production of all neurons (Kandel 2006). Neural stem cells in the embryonic and post-natal stages give rise to neurons and glial cells (Urban and Guillemot 2015). It was believed to be limited to embryonic development and perinatal stages in mammals for many years (Ming and Song 2005). It was traditionally believed that NSCs were depleted perinatally (Jin 2016). Nonetheless, newly generated dentate granule cells (DGCs) and multipotent NSCs derived from adult mammalian brain were detected by Altman and Das (1965). Altman's discovery was however ignored until the 1970s-1980s when Kaplan and Hinds (1977) discovered new born cells in the adult mice brain. Furthermore, Goldman and Nottebohm (1983) demonstrated the presence of new born cells in brain of adult canaries, as well as showed that these cells had ultrastructural characteristics of neurons (Sierra et al. 2011).

Neuronal replication in the adult was considered unlikely because most neurons are complex; with highly branched dendrites and polysynaptic axonal combinations (Gage 2002). It was also thought that if neurons were able to divide, the newly created cells with their new dendrites, axons, and synapses, would not be able to integrate into the already existing circuits in the brain without disrupting them (Gage 2002).

Evidence of adult neurogenesis was improved by the development of immunohistochemical techniques for labelling proliferating cells with nucleotide analogs

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such as bromodeoxyuridine (BrdU), protein markers that were specific to neurons such as NeuN and confocal imaging (Aimone et al. 2014). It is now well established that new neurons are continuously generated by stem cells in at least two discrete regions in the brain throughout life in most mammals: the hippocampus and the olfactory bulb (Ernst and Frison 2015). Recent evidence has established neurogenesis in the adult brain in other areas such as the neocortex, cerebellum, striatum, amygdala and hypothalamus (Radad et al. 2017). In adult mammals, the specific areas that neurogenesis persists are known as neurogenic niches (Urban and Guillemot 2015).

REGULATION OF ADULT NEUROGENESIS

Adult neurogenesis is regulated by physiological and pathological activities at all levels which include the proliferation of adult neural stem cells (NSCs) or progenitors, differentiation and fate determination of the progenitor cells, survival, maturation and integration of new born neurons into existing neuronal circuits (Zhao et al. 2008; Liu and Song 2016). Several signals which range from excitation to systemic factors and drugs capable of crossing the blood brain barrier cluster around neural stem cells present in the neurogenic niches (Hsieh and Zhao 2016).

Cell proliferation: Neural stem cells proliferate giving rise to identical daughter cells (Li et al. 2017). Majority of these cells remain quiescent until they are activated by either intrinsic or extrinsic factors (Jin 2016; Li et al. 2017). Quiescent neural stem cells become activated to generate transit amplifying cells (TACs) and transient intermediate progenitors (TIPs) (Liu and Song 2016) that enlarge the pool of the neurogenic cells: type-2 cells in the dentate gyrus (DG) and C-cells in the subventricular zone (SVZ) (Braun and Jessberger 2014). The activated cells divide asymmetrically to enrich a pool of amplifying neuroprogenitors (ANP). Adult NSCs already divided need to up-regulate transcription factors and acquire measurable protein levels to proceed to neurogenesis; failure of which leads to gliogenesis (Gotz et al. 2016); although the formation of astrocytes and oligodendrocytes is not restricted to the subventricular zone (SVZ) and the subgranular zone (SGZ) but continues throughout the mature CNS (Duan et al. 2008). The hedgehog signalling pathway is activated in quiescent adult neural stem cells helping to maintain the proper NSC pools in the DG and SVZ (Antonelli et al. 2019). Leukemia Inhibitory factor expression helps in the promotion of adult NSC self-renewal and prevents their differentiation (Duan et al. 2008).

Fate determination of the progenitor cells: Fate determination of adult NSCs is likely to be regulated by neurogenic niche signals (Duan et al. 2008). After a limited number of divisions, the TACs and TIPs give rise to neuroblasts (Liu and Song 2016). The proliferating neuroblasts then leave the cell cycle, a subpopulation of which survives, differentiating into new-born neurons that will then be integrated into the existing neuronal circuit in the brain (Kempermann et al. 2004; Liu and Song 2016). Immature neurons migrate into the granule cell layer of the dentate gyrus to mature into granule cell neurons; they then begin to grow apical and basal dendrites into the adjacent molecular layer and axons that innervate the CA3 of the hippocampus (Braun and Jessberger 2014; Jin 2016).

Survival and maturation of new-born neurons: Several transmembrane factors and intracellular signalling molecules, such as notch signalling help in the regulation of cell survival/cell death decision (Liu and Song 2016; Pfisterer and Khodosevich 2017). These factors are known as pro-survival factors and they depend on the type of neuron and the region of the brain (Pfisterer and Khodosevich 2017). The rate of maturation can be correlated with the pattern of neuronal activity (Piatti et al. 2011). Piatti et al. (2011) found a slow pace of development in the temporal dentate gyrus of sedentary mice while high network activity in the septal dentate gyrus and in both septal and temporal dentate gyrus of running mice promotes high maturation rate. This suggests that physical exercise such as running enhances the survival and maturation of new born neurons (Baptista and Andrade 2018).

Integration of new born neurons into existing circuits: Functional integration of new born neurons has been studied through the use of engineered oncoretrovirus and transgenic reporter mice (Duan et al. 2008). Synaptic integration is significantly slower in adult neurogenesis than it is during embryonic and postnatal neurogenesis (Ge et al. 2008). After migration, connections are established by the new-born granule cells in the adult hippocampus from tonic activation by ambient ɣ– aminobutyric acid (GABA) which occur only on dendrites and cell bodies in the granule cell layer (Ge et al. 2008, Jin 2016). This is followed by dendritic glutamatergic inputs and finally perisomatic GABAergic inputs (Ge et al. 2008).

ARGUMENTS FOR AND AGAINST ADULT NEUROGENESIS

As established from various studies, adult neurogenesis exists in two sites in the brain: the SVZ of the DG of the hippocampus and the olfactory bulb; although there are other non-canonical sites (Ernst and Frison 2015). Despite this, arguments still ensue that claims that adult neurogenesis does not occur in the human hippocampus.

The first report of adult hippocampal neurogenesis in humans was provided by Eriksson et al. (1998) who

established the gold standard method on the human hippocampus using BrdU for tumor-staging purposes. The study established the detection of adult neurogenesis in the same location as that of rats (Kempermann et al. 2018).

Sorrells et al. (2018) concluded that adult neurogenesis does not occur in the human brain beyond seven years of life and that neuroblasts decreased with increasing age. The study concluded that the recruitment of young neurons to the primate hippocampus decreases rapidly during the first years of life and that it doesn't continue or is extremely rare in adult humans. This infers that the human hippocampus likely functions differently from that of other species.

Conversely however, from the autopsy of healthy human individuals ranging from 14 to 79 years, there was similar number of neural progenitors in the DG suggesting that hippocampal neurogenesis is a lifelong occurrence. The decline in cognitive function in ageing may be linked to compromised cognitive-emotional resilience (Boldrini et al. 2018). Capriani et al. (2018) showed persistence of neural stem cells and progenitor cells in the adult brain but the absence of actual neurogenesis.

Within a few weeks of each other, several opposing conclusions had arisen concerning the presence of neurogenesis in the adult human hippocampus. However, several other studies have been carried out to uphold or disprove these studies. Both Boldrini et al. (2018) and Sorrells et al. (2018) based their main conclusions on the expression of key marker proteins such as doublecortin (DCX) and polysialylated NCAM, (PSA-NCAM), the embryonic form of neural cell adhesion molecule (Kempermann et al. 2018). Marker expression shows supportive evidence of adult neurogenesis, whose validity has been questioned. The disparity in results might be because Sorrells et al. (2018) obtained tissues from chronic epilepsy patients, whereas Boldrini et al. (2018) obtained post-mortem tissues from individual with no psychiatric disorders (Lima and Gomes-Leal 2019). Epilepsy has been reported to result in a massive reorganization of the hippocampal circuitry and damage to the neurogenic niche influencing the amount of neuroblasts present in the hippocampus (Jessberger and Parent 2015). Post-mortem delay could also be responsible for the differences in the results of both studies (Kempermann et al. 2018). Sorrells et al. (2018) examined their tissues after 48 hours, while Boldrini et al. (2018) examined theirs at about 26 hours. Another likely reason for the discrepancy could be the fixation protocol employed for the brain samples. Over fixation may inhibit immunolabelling for DCX (Lima and Gomes-Leal 2019). Boldrini et al. (2018) used more sophisticated equipment and made use of stereology, a more sophisticated technique for cell counting which makes it more accurate. This study was later corroborated by Moreno-Jimenez et al. (2019) which reported the presence of thousands of new neurons in the adult hippocampus.

Although adult neurogenesis research has been carried out in laboratory rodents, these models are too simple considering the different species-specific adaptations and the neuroanatomy of different animals (Parolisi et al. 2018). Rodents show a decline in adult neurogenesis with age (Kuhn et al. 1996; Kuhn et al. 2018), some bats also show substantial reduction in adult neurogenesis (Parolisi et al. 2018). Adult neurogenesis seems absent in cetaceans (Amrein 2015) while in dolphins, neurogenesis disappears both in postnatal and adult lives (Parolisi et al. 2018). Petrik and Encinas (2019) suggested that it could be that the neuronal maturation process is much slower in humans and that the ratio between cell proliferation and maturing neurons is much weaker than in mice..

FACTORS AFFECTING NEUROGENESIS

The stages of neurogenesis are controlled by genetic and molecular factors thus, establishing a similarity between adult and embryonic neurogenesis (Baptista and Andrade 2018). There are also intrinsic and extrinsic factors that can increase or suppress adult neurogenesis depending on human behaviour and the surrounding environment (Kempermann 2011).

Intrinsic Factors

Epigenetic factors: Epigenetic factors are molecules that modify gene expression via DNA methylation, histone modification, chromatin remodelling, noncoding RNAs (Hsieh and Zhao 2016) and miRNAs (Alegria-Torres et al. 2011). These modifications in gene expression are heritable but are termed epigenetic because they do not involve DNA mutation (Liu and Song 2016). They have been reported to play key roles in neural stem cell renewal, fate specification and final maturation of new neurons (Hsieh and Zhao 2016). Epigenetic factors reported to regulate adult neurogenesis include methyl-CpG-binding domain protein 1 (Mbd1), histone deacetylase 2 (HDAC2) and microRNAs (Liu and Song 2016). Also, various transcription factors including sex-determining region Y-box 2 (Sox2), Orphan nuclear receptor TLX, forkhead box O proteins (FoxOs), prospero homeobox 1 (Prox1), neuronal differentiation (NeuroD), Kruppel-like factor 9, paired box protein (Pax6), and neurogenin 2 (Neurog2) were found to regulate adult neurogenesis (Braun and Jessberger 2014; Liu and Song 2016).

Molecular Factors: Several molecular factors have been known to regulate specific stages of adult neurogenesis (Liu and Song 2016). Growth factors such as epidermal growth factor (EGF), brain derived growth factor (BDGF) and fibroblast growth factor (FGF2) are potent factors for the maintenance of adult NSCs *in vivo* and *in vitro* because they promote

proliferation of adult NSCs in the SVZ (Zhao et al. 2008).

Morphogens are extracellular signalling molecules known for their roles in embryonic patterning and axis formation during development (Liu and Song 2016). Several morphogens have been involved in establishing/regulating the stem cell niche, including notch, sonic hedgehog, Wnt/β-catenin, and bone morphogenetic proteins (Choe et al. 2016). Neurotransmitters such as gamma-aminobutyric acid, dopamine, glutamate, and serotonin have been shown to affect adult neurogenesis via their proliferation and differentiation of cells within neurogenic zones (Faigle and Song 2013; Braun and Jessberger 2014). NSCs in the SVZ express glutamate receptors (NMDA, kianate, metabotropic glutamate receptors) where glutamate signalling can promote cell proliferation (Young et al. 2011). Excitatory stimulation of NMDA receptors on adult hippocampal NSCs result in increased intracellular calcium and activation of the proneural gene, NeuroD1, highlighting direct effects of glutamate on adult neuroprogenitor cells (Sibbe and Kulik 2017). In the same vein, an α-2adrenergic agonist has also been found to increase adult neurogenesis by increasing the survival and differentiation of new neuroblasts (Hagg 2009). Similarly, the paracrine activation of $GABA_A$ receptors on NSC populations by their progeny has been shown to have a non-synaptic inhibitory effect on proliferation and may act as a negative feedback mechanism to modulate proliferation in adult and post-natal brains (Liu et al. 2005). The *in vivo* administration of $GABA_A$ receptor agonists (phenobarbital) resulted in reduced NSC proliferation and increased differentiation leading to enhanced numbers of newly generated neurons (Tozuka et al. 2005).

External Factors

The most studied positive external regulators of adult neurogenesis include olfactory and hippocampal learning, physical activity and environmental enrichment (Braun and Jessberger 2014). Cognitive stimulation such as baking, solving puzzles amongst other activities in humans can regulate the processes of adult-born neuron production (Jin 2016). Physical exercise such as voluntary running, can also promote SGZ cell proliferation in adult animals and rescue impaired hippocampal neurogenesis (van Praag et al. 1999).

Age is also a factor that affects neurogenesis. Neurogenesis declines steadily during aging in rats. After an initial peak around the second postnatal week, neurogenesis declines during adolescence and continues to decline during adulthood and senescence in rats (Kuhn et al. 1996). In the same vein, cell proliferation in the SVZ of the lateral ventricle and in the DG of the hippocampus was reportedly lower in adult African giant rats compared to juveniles (Olude et al. 2014). However, Boldrini et al. (2018) reported that adult human hippocampal neurogenesis persists throughout aging. Chawana et al. (2020) observed variation in adult hippocampal neurogenesis in Egyptian fruit bats from different environments.

ADULT NEUROGENESIS IN BRAIN DISEASES

Neurodegenerative disorders are a heterogenous group of diseases that are characterised by progressive breakdown of the structure and function of the nervous system. Adult-born neurons may play significant physiological roles in hippocampus-dependent functions such as memory encoding (Toda et al. 2019). Loss of neurons in an adult brain has been documented as basis for many neurodegenerative diseases (Ihunwo et al. 2016).

Altered epigenetic regulation has also been found to result in various neurological disorders (Hsieh and Zhao 2016). Also, some symptoms of various neurological diseases and mood disorders can be explained by defects in adult hippocampal neurogenesis (Toda et al. 2019).

Neurodegenerative disorders such as Alzheimer's, Parkinson's, Huntington's diseases, transmissible spongiform encephalopathies (bovine spongiform encephalopathy in cattle, scrapie in sheep) and stroke in animals include the loss of different neural populations (Winner and Wegner 2015). Thus, modulation of neurogenesis can provide possibility for structural and functional plasticity in the adult brain representing a potential therapeutic target for brain repair (Jin 2016).

Stroke

Stroke is caused by the occlusion of the cerebral artery which leads to the obstruction of cerebral blood flow leading to ischaemia and death of vulnerable neuronal populations (Lindvall and Kokaia 2015). Several experimental procedures have demonstrated that a stroke-damaged brain tries to repairs itself through the production of new neurons especially in the areas of the brain where adult neurogenesis does not usually occur, such as the cerebral cortex (Ernst and Frison 2015; Lindvall and Kokaia 2015; Jin 2016). The mechanisms involved in stroke-induced neurogenesis include proliferation of neural stem/progenitor cells, survival of new-born neurons and migration of new neuroblasts to injured areas, as well as differentiation and functional integration of new neurons (Jin 2016). The process is regulated by a wide variety of signalling pathways (Lu et al. 2017). Most newly born cells undergo apoptosis during the first two weeks after birth. Thus, improving the survival of new cells may be the key strategy to promote neurogenesis after stroke (Lu et al. 2017). Administration of erythropoietin (Wang et al. 2004) and NSC transplantation (Tang et al. 2014), promote neurogenesis after stroke and is associated with improved behavioural recovery. This suggests that

enhancement of adult neurogenesis can be targeted in the management of stroke.

Alzheimer's Disease

Alzheimer's disease (AD) is predominantly characterized by progressive neuronal loss, followed by memory loss and cognitive impairment which can be predicted by olfactory sensitivity and odour discrimination (Suzuki et al. 2004). Some studies have found reduction of neuronal progenitor proliferation with BrdU labelling in aging rats and in AD mouse models. Apolipoprotein E4, the major known risk factor for AD, inhibits hippocampal neurogenesis by impairing the functions of GABAergic interneurons (Li et al. 2009). Bolognin et al. (2012) found that peptide 6 corrected cognitive impairment in 12N-terminal fragments and C-terminal fragments (I2NTF-CTF) rats, which exhibited abnormal hyperphosphorylation and aggregation of tau, synaptic loss, and impaired spatial reference and working memories, by increasing hippocampal neurogenesis. This suggests that hippocampal neurogenesis ameliorates cognitive dysfunction associated with AD in animal models.

Parkinson's Disease

Parkinson's disease (PD) is a progressive, chronic neurodegenerative disorder associated with the degeneration of dopaminergic neurons of the substantia nigra (Liu and Song 2015). The pathological hallmarks of PD are accumulation of alpha-synuclein and intracellular deposits to form inclusion bodies known as Lewy bodies and filamentary Lewy neuritis (Stefanis 2012). PD affects the neuronal activities at various regions of the brain such as the amygdala, hippocampus, and olfactory bulb (Hoglinger et al. 2004). The number of neural precursor cells decrease with the olfactory bulb volume unchanged in some studies but reduced in others (Hoglinger et al. 2004; Hummel et al. 2010).

In genetic animal models and human post-mortem studies, hippocampal atrophy and disruption in hippocampal neurogenesis are related to PD (Lim et al. 2018). These hippocampal deficits may be responsible for the non-motor symptoms such as hyposmia, lack of novelty seeking behaviour, depression and anxiety that are associated with the disease. It is therefore conceivable that some of these non-motor deficits are related to a defect in adult neurogenesis (Maxreiter et al. 2013).

A study in the PD mouse model showed that the engraftment of NSCs led to differentiation into dopaminergic neurons and migration of the neurons into the substantial nigra (Shohayeb et al. 2018).

Conclusion

Recent findings that new neurons are generated in adults have challenged previously held concepts of brain plasticity and it is now established that new neurons are continually generated in distinct regions of the adult brain. The factors that regulate adult neurogenesis have also been extensively discussed. The potential of enhancing the neurogenic process lies in improved brain cognition and neuronal plasticity particularly in the context of neurological and neurodegenerative disorders. Novel therapies that enhances cognition and enhance the integration of new neurons into existing circuits may be beneficial in the treatment of neurodegenerative disorders. However, the cellular and molecular mechanisms that guide the progression from a dividing NSC to a functional neuron need to be better understood in details.

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