New neurons in the adult hippocampus: Hope or hype?

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CLINICAL POINTS

- Adult neurogenesis is the generation of functional neurons from neural stem cells present in the adult.
- Adult hippocampal neurogenesis occurs in the subgranular zone of the dentate gyrus, a central component of the hippocampal neural network.
- Adult neurogenesis is stimulated by specific types of learning, exercise and neurotrophic factors such as BDNF and Shh. It is downregulated by corticosteroids, inflammation and some drugs.
- Recently, several epigenetic mechanisms have been found to regulate neurogenesis and the maturation of new neurons.
- Upregulation of neurogenesis has been implicated in the molecular mechanism of action of treatments for depression (e.g. antidepressant drugs and ECT); possible future applications include treatment of stroke and traumatic brain injury.

ABSTRACT

Stem-cell research has caused a paradigm shift in our understanding of brain function and regeneration. Discovery of the production of functional neurons in the adult hippocampus, a neurogenic niche of the central nervous system (CNS), has refuted the long held theory proposed by Ramon y Cajal that in the CNS "everything may die, nothing may be regenerated". Neurotrophic factors, activity-dependent neurogenesis, downregulation factors and post-translational regulatory mechanisms seem to interact in a complex and still ill-explored fashion to control this endogenous regenerative process. Moreover, in animal models, upregulation of neurogenesis is achieved with fluoxetine and other antidepressant therapies such as electroconvulsive therapy (ECT), demonstrating the clinical relevance of this mechanism. In fact, recent studies suggest that the upregulation of neurogenesis might also provide treatments for conditions such as traumatic brain injury (TBI) and stroke.

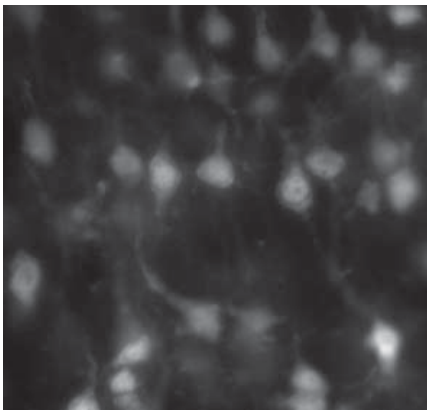


Figure 1:

Immunofluorescent microscopy from rat hippocampus tissue where NeuN was used as a marker and mature neurons can be clearly visualized. This technique and double or triple marker techniques provide an easy and reliable protocol to count different types of cells in hippocampal tissue. Image collected by the author in the Institute of Neuroscience, Trinity College, Dublin.

INTRODUCTION

Stem cells are distinct from most other cells in the body due to their ability to both proliferate indefinitely and to generate a variety of differentiated cell types. In a similar manner to haematopoietic stem cells that produce red blood cells, white blood cells and platelets, neural stem cells can differentiate into the main cells of the CNS: neurons, astrocytes and oligodendrocytes[1-2]. Neurogenesis is the production of mature neurons from neural stem cells. This process was detected in adult humans only a decade ago[3-5], but has since been confirmed in two distinct regions of the brain: the subventricular zone and the dentate gyrus of the hippocampus[6]. The newly formed immature neurons begin expressing a series of transient markers, such as doublecortin, followed by later markers like neuronal nuclear protein (NeuN), present in fully differentiated neurons (see Figure 1). During the differentiation process, dendrites develop within the hippocampal network by initially forming synapses at dendritic shafts and later forming more mature synapses with dendritic spines such as thorny excrescences[7-8]. van Praag et al[9] and others have shown that these neurons are functionally relevant in a key area of the brain involved in memory and emotion – the hippocampus[9-11]. This review provides an introduction to the function and neurogenic properties of the hippocampus followed by an analysis of the regulatory mechanisms of neurogenesis and the possible clinical applications of its stimulation in several neurological conditions.

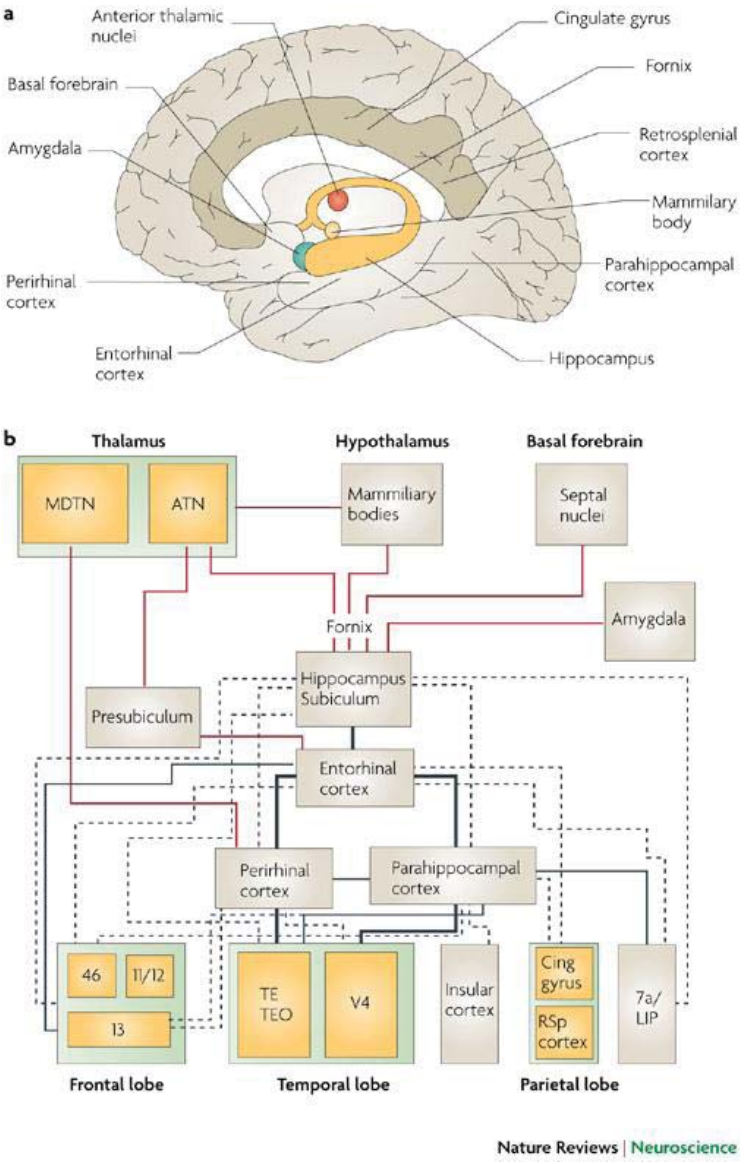


Figure 2: The hippocampus is connected to cortex regions (represented by black lines) and subcortical structures such as anterior thalamic nuclei (ATN), medial dorsal thalamic nuclei (MDTN) and others (represented by red lines). Figure reproduced from Bird C, Burgess N. The hippocampus and memory: insights from spatial processing. Nature Reviews Neuroscience. 2008; 182-94.

STRUCTURE AND FUNCTION OF THE HIPPOCAMPUS

The hippocampus includes the hippocampus proper, the subiculum and the dentate gyrus and maintains an anteroposterior functional specialization pattern. The ventral (anterior) part has been linked to emotionality whilst the dorsal (posterior) part is associated with learning[12-13]. Other studies, using functional magnetic resonance imaging (fMRI), have shown how ventral hippocampal activity is associated with the processing of novel stimuli. This activity gradually shifts to the dorsal hippocampus as these stimuli become more familiar, suggesting that the latter region is associated with long-term memory[14]. Moreover, left-right asymmetry is found in the hippocampus since the anterior left hippocampus is associated with new language material while the right hippocampus is involved in spatial activities such as driving a car[15]. All of these different functions are enabled by the large and diverse set of connections between the hippocampus and other brain regions (see Figure 2).

THE HIPPOCAMPUS: A NEUROGENIC NICHE

Neurogenesis within the hippocampus is supported by its diffuse neuronal connections to other regions of the brain and the characteristics of the hippocampal dentate gyrus, where neurogenesis takes place. The hippocampus receives cholinergic, noradrenergic, serotonergic and dopaminergic connections, most of which pass through the hippocampal fornix. These inputs appear to be important for synaptic plasticity and adult hippocampal neurogenesis[16]. For example, inhibition of serotonin production with the drug parachlorophenylalanine (PCPA) is associated with a reduction in the number of new neurons produced in the dentate gyrus[17].

The dentate gyrus receives connections from the entorhinal cortex and projects efferent connections of unmyelinated granule cell axons (mossy fibers) through the fornix, thereby playing a fundamental role in the hippocampal neuronal network[18]. Its particular properties include the specific functions of astrocytes and capillaries which seem to create a "neurogenic niche". Thus, the dentate gyrus is a microenvironment within the CNS that has unique characteristics allowing for the differentiation of neural progenitors and their integration into the neural circuitry.

Vascular endothelial growth factor (VEGF), a well characterized angiogenic factor, appears to stimulate neurogenesis in the dentate gyrus[19]. This supports the concept of the neurogenic niche as also a "vascular

niche," a dynamic biochemical microenvironment of angiogenesis and vascular remodelling. In fact, Palmer et al[20] found that in vivo areas of high neural stem cell proliferation are in close proximity to dentate gyri capillaries which suggests an overlap between angiogenic and neurogenic mechanisms in the adult brain.

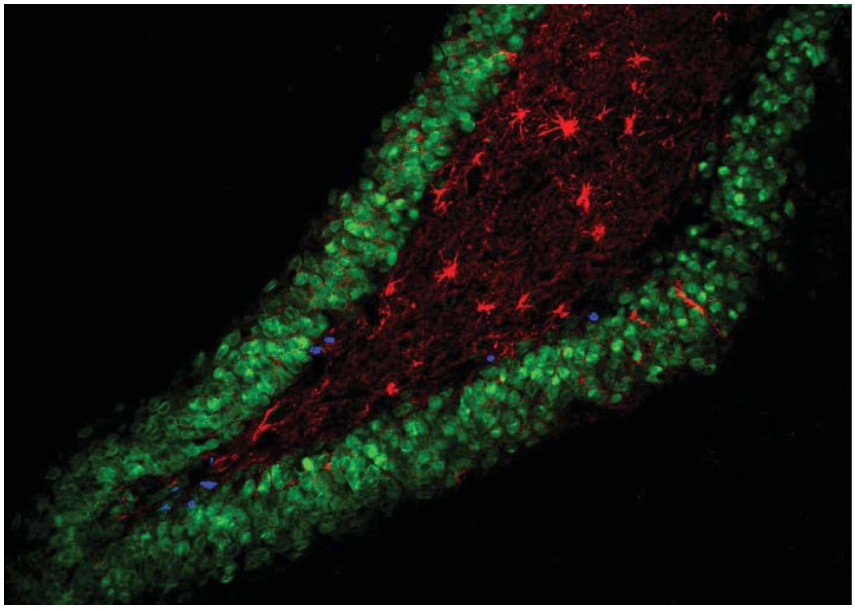
Similarly, astrocytes, now considered the most important non-neural cells involved in regulating neurogenesis, are apposed to the subgranular zone of the dentate gyrus – the zone where neurogenesis takes place (see Figure 3)[21-25]. They promote proliferation and neuronal specification of adult neural stem cells in vitro whereas astrocytes from non-neurogenic areas such as the spinal cord do not. This view is supported by their unique ability to produce neurogenic signals, such as neurogenesin-1, a neuronal cell fate factor that promotes the specialization of neural stem cells into neurons rather than astrocytes[26].

Moreover, certain activities can influence this neurogenic niche. Besides the special properties of astrocytes and angiogenesis in the dentate gyrus which allow for a basal level of neurogenesis, certain types of learning or simple physical exercise have been shown to upregulate hippocampal neurogenesis.

ACTIVITY-DEPENDENT NEUROGENESIS

It is now commonly accepted that adult neurogenesis in the hippocampus is stimulated by local factors such as nearby synaptic activity and systemic factors including some hippocampal-dependent types of learning and physical exercise.

On a synaptic level, there is in vitro evidence for the direct stimulation of neural stem cells through glutamate NMDA receptors and Cav1.2/1.3 channels. Administration of antagonists such as nifedipine to these L-type calcium channels causes a complete block of excitation-induced neurogenesis in rodent models[27]. Moreover, antagonizing NMDA receptors in neural stem cells in vitro blocks both excitation-induced neurogenesis and basal neurogenesis levels[27]. Paradoxically, indiscriminate NMDA glutamate receptor agonist binding seems to reduce neurogenesis in vivo. It is postulated that this effect is mediated by inhibitory GABAergic hippocampal interneurons activated by NMDA glutamate receptors[28-29]. Hence, there is a counterbalance to excitation-induced neurogenesis mediated by GABAergic interneurons.



▲ **Figure 3:** Unlike the remainder of the hippocampal formation, populated by pyramidal cells, the dentate gyrus has granular cells and is composed of the subgranular zone, containing the neural progenitors (blue) responsible for adult neurogenesis, and the outer granular and molecular layers with granular cells (neurons) in green. In this rat brain slice, astrocytes (red) were also marked. This photo was taken in the lab of David Schaffer at the University of California, Berkeley.

The evidence for the stimulation of neural stem cells through NMDA and Cav1.2/1.3 channels demonstrates how neurogenesis is influenced by neuronal activity at a cellular level. Conversely, behavioural data obtained by Shors et al[30] shows that some types of learning are dependent on adult neurogenesis. Hippocampal-dependent types of learning include trace fear conditioning (formation of memories of noxious events) and spatial learning (measured in rodents using a Morris water maze exercise). This study found that only some of these types, such as trace fear conditioning, are dependent on active adult hippocampal neurogenesis suggesting a significant but complex role of adult neurogenesis in hippocampal-dependent learning[30-31].

Similarly, rodent studies looking at the effects of physical exercise on neurogenesis and cognition provide a basis for an exercise-induced neurogenesis hypothesis[32-33]. Through future research, these results might help to explain human cohort data identifying a correlation between cardiovascular fitness and cognition levels[34-35].

Recent studies have also linked the regulation of adult hippocampal neurogenesis with leptin[36], diet[37] and sleep patterns[38]; suggesting that some factors of overall health and lifestyle may influence brain func-

tion by regulating neurogenesis. Although the interplay of all of these factors in the process of neurogenesis is not completely understood, much is known about the mechanisms involved in its control, which include both neurotrophic and downregulation factors.

NEUROTROPHIC FACTORS

A neurotrophic factor is any regulatory factor present in the CNS that upregulates neurogenesis. These include VEGF, fibroblast growth factors 1 and 2 (FGF-1 and FGF-2), oestrogen and endothelial growth factor (EGF). However, two of the most studied and well understood are the brain derived neurotrophic factor (BDNF) and Sonic hedgehog (Shh).

BDNF promotes the differentiation and survival of new neurons in the adult and is essential for the development of the embryonic CNS. A reduction in BDNF is thought to play a role in neurodegeneration, chronic stress and depression[39]. BDNF binds to TrkB, a tyrosine kinase receptor, thereby activating a series of molecular cascades which are fundamental for normal hippocampal structural development. For example, one of these pathways includes mitogen-activated protein kinase kinase (MEK) and extracellular regulated kinase (ERK)[40]. The transcription of BDNF is regulated by calcium/cyclic-AMP responsive-element binding protein (CREB), itself phosphorylated by this MEK-ERK pathway, thus establishing a positive feedback mechanism. Stressful environments, as replicated in animal models, are associated with a down regulation of BDNF mRNA and protein levels[41-43]. Similarly, CREB has been shown to be down regulated in the cerebral cortex of depressed patients and to be reduced in the dentate gyrus following stress. It is thought that most antidepressants achieve their effect through the upregulation of the CREB-BDNF pathway and possibly subsequently through hippocampal neurogenesis[39-44].

Similarly, Shh not only promotes early neural development in the embryo but also promotes survival of stem cell niches in the adult brain. While its role is not yet completely understood, Shh has been shown to elicit a dose-dependent proliferation in neural progenitor cells both in vitro and in vivo. In fact, blocking Shh signalling reduces hippocampal neural stem cell proliferation in vivo[45-46].

DOWNREGULATION

Downregulators of hippocampal neurogenesis such as nicotine, opiates, alcohol, endogenous glucocorticoids and IL-6 have an opposite effect to that of neurotrophic factors[28]. The inflammatory marker IL-6 is particularly interesting since it counteracts a compensatory increase in neurogenesis following neuronal death and inflammation caused by TBI (see Clinical Uses for further discussion). In the rodent model, transgenically induced astroglial production of IL-6 reduced hippocampal neurogenesis by 63% possibly through autocrine and/or paracrine mechanisms[47]. Furthermore, the action of glucocorticoids provides a mechanism that explains how overactivity of the hypothalamo-pituitary-adrenocorticoid axis, present in patients suffering from depression, might be partially responsible for the lower levels of neurogenesis observed in these patients[48].

In addition to these regulators of neurogenesis, there are also mechanisms that control neurogenesis at an upstream level by means of post-translational control of gene expression.

POST-TRANSLATIONAL REGULATORY MECHANISMS

Post-translational regulatory mechanisms, such as epigenetics and microRNA (mi-RNA), influence gene expression without altering the DNA sequence present in all somatic adult cells. As a result, these mechanisms control the production of regulatory factors and the ultimate fate of neural stem cells.

Epigenetic control mechanisms are post-translational modifications of DNA and nuclear proteins that produce permanent changes in chromatin structure and therefore regulate gene expression[49]. Several epigenetic regulatory mechanisms of neurogenesis have been identified in the past decade[50-51] such as DNA methylation[52]. DNA methylation is a well understood post-translational modification that involves the addition of methyl groups to lysine residues of chromatin by DNA methyltransferases. This reduces the transcription of these methylated genes, a process referred to as gene silencing. There are also proteins which demethylate promoter regions thereby allowing for the transcription and expression of the previously methylated genes. Ma et al concluded that the Gadd45b gene, expressed in mature neurons, was required for the demethylation of BDNF and FGF-1 promoters thereby allowing these neurotrophic factors to be transcribed. Gadd45b gene knockout in a rodent model caused a significant reduction in activity-induced neurogenesis and dendritic development[52].

Another post-translational mechanism regulating neurogenesis involves miRNA and was identified by Cheng et al using rodent models. miRNAs are 22-nucleotide-long non-coding RNA sequences that cause the degradation or inhibition of complementary sequences of mRNA

thereby reducing gene expression[53]. This mechanism regulates neurogenesis in the subventricular zone rather than the hippocampus; however, it provides an example of what might underlie neurogenesis control in all neurogenic niches of the CNS. In this study, miRNA miR-124, which causes the downregulation of the transcription factor Sox9, was suggested to be important for adult neurogenesis. Sox9 stimulates glial cell formation from neural stem cells. miR-124 reduces Sox9 expression, thereby promoting an alternative cell fate: neurogenesis. Hence, miR-124 increases the proportion of neurons to glial cells produced from the proliferating neural stem cells and functions as a "neuro-glial cell fate switch" [54-56].

The mechanisms of epigenetic control of neurotrophic factor production and the mi-RNA based "neuroglial cell fate switch" help us to better understand the process by which cells differentiate and integrate into a complex network such as the CNS. While the clinical potential of these post-translational mechanisms is unknown, other areas of research into adult neurogenesis have already discovered several clinical implications.

CURRENT AND FUTURE CLINICAL IMPLICATIONS

Upregulation of neurogenesis has been inadvertently used as the mainstay of treatment for depression for decades until its role was brought to light by Santarelli et al. Their study showed that selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, did not have an antidepressant effect in animals where neurogenesis was eliminated by selective irradiation of the hippocampus[44]. Hence, the first clinical application of the upregulation of neurogenesis was identified.

In current clinical practice, the treatments that involve upregulation of adult hippocampal neurogenesis are used solely for depression. These include some antidepressants, such as fluoxetine[31], and electroconvulsive therapy (ECT)[57], used in cases of severe depression refractory to conventional pharmacotherapy. The antidepressant effect of ECT seems to be mediated in part by increased VEGF production. This provides a possible explanation for the efficacy of ECT in cases where pharmacological antidepressants do not work because these agents do not increase VEGF production[28,58]. In fact, the clinical use of ECT might be improved in the near future as some small clinical trials, which have focused on fine-tuning the electrical pulse width and electrode placement, have shown increased treatment efficacy and a reduction of its classic side-effects including retrograde amnesia[59].

Another important therapeutic goal for the future is to discover a treatment that would upregulate endogenous neurogenesis after TBI or stroke, hence improving motor and cognitive patient outcomes. It is known that VEGF-induced neurogenesis10 is part of the endogenous repair response to ischaemic stroke in the adult cortex[60] even though it is not clear to what extent cortical neurogenesis is present in adult humans[6]. While adult cortical neurogenesis is significant in vertebrates like fish, amphibians and reptiles, it seems to have been suppressed throughout evolution in birds and mammals[61].

A complete understanding of the necessary conditions for the upregulation of functionally significant neurogenesis after stroke or TBI has not yet been reached. Nevertheless, promising experiments using doublecortin and NeuN markers have shown new hippocampal neurons to migrate to ischaemic striatal areas after induced ischaemic events in rodent models[62-63]. Unfortunately, these new neurons have minimal survival rates in their new location. As a result, the clinical significance of these migratory neurons is limited until the necessary conditions for their integration into functional networks are discovered[62-64].

A caveat for possible future treatments involving the upregulation of neurogenesis is the risk of deregulated neurogenesis. Results from González-Martínez et al[65] suggest that spontaneous neurogenesis is associated with pharmacoresistant human neocortical epilepsy. Nevertheless, it is still unclear whether this is related to its pathogenesis or an endogenous mechanism of repair that fails to function in this condition.

Moreover, it has been shown that it is possible to improve sensorimotor and learning outcomes by upregulating neurogenesis after damage to the mammalian cortex. For example, Shear et al[66] used mammalian models to transplant exogenous neural stem cells after TBI. They reported positive behavioural and motor outcomes, providing a basis for future use of neural stem cells in a wide range of pathologies[66-67]. Another method by which this might be achieved was demonstrated by Xiong et al[68]. This study concluded that administration of erythropoietin six hours post-TBI provided neuroprotection and neurorestoration by enhancing neurogenesis, angiogenesis and synaptic plasticity in the dentate gyrus of a rodent model. More importantly, erythropoietin improved sensorimotor and spatial learning outcomes[68]. The biochemical mechanism of erythropoietin has been studied in the subventricular zone and it appears to upregulate BDNF and VEGF production[69]. Nevertheless, erythropoietin, after an early successful clinical trial[70], was tested in a randomized multicenter trial which has shown that it is not acceptable for use in stroke

due to an increase in mortality at 90 days post stroke[71-72]. Therefore, while we know that it is possible to upregulate neurogenesis with positive clinical outcomes, no drug that will safely do so has yet been discovered.

CONCLUSION

The discovery of adult neurogenesis in key regions of the CNS such as the hippocampus has changed our understanding of brain function and repair[73]. The previous model of a fixed adult neuronal circuitry, similar to a computer circuit board, may be replaced by a model of a more dynamic nature, constantly adapting to exogenous and endogenous signals[74]. Moreover, current knowledge of the regulatory mechanisms involved in neurogenesis allows us to understand the mechanisms of action of some treatments for depression and provides a new framework for research on treatments for many common neuropsychiatric and neurological disorders, including stroke and TBI. Hence, the discovery of adult neurogenesis will probably change the way we treat brain injury as much as it has changed our understanding of how the brain functions.

ACKNOWLEDGMENTS

My thanks to Prof. Declan McLoughlin and Sinead O'Donovan of the Department of Psychiatry and Trinity College Institute of Neuroscience CIN) for all the guidance and support provided during my research elective last summer.

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