

Manipulation of Neural Stem Cells as a Rehabilitative Therapy

The brain develops from stem cells that are born in the medial and lateral ganglionic eminences, migrate towards the pia matter and reside in regionally specific regions of the brain where they differentiate to form neurons and glial cells. Until the last decade the common belief has been that after development ceases, no new neurons are produced in the brain. In reality, new neurons are continually produced in the brain throughout the life of mammals. In response to intrinsic cell death in a particular brain region or as a result of external stimuli, differential regulation of brain-harboured stem cells occurs. Thus in general terms, the stem cell niches in the adult brain remain sensitive to internal and external stimuli encountered by the individual, and this unique function continues throughout life.

The stem cell niches in the adult brain

In the mammalian brain there are two stem cell/neurogenic niche regions: the subventricular zone (SVZ) near the basal ganglia and, the subgranular zone (SGZ) of the hippocampus. In the adult brain, neurogenesis continues in the SVZ throughout adult life, providing ongoing cell replacement in the forebrain, particularly in the olfactory bulb.¹ The proliferation-permissive environment, some fate determinants, and the direction of migration of stem cells are at least, in part, determined in the SVZ.^{2,3} The biology of the SVZ in the normal and diseased human brain demonstrates, similar to the rodent, that the SVZ retains a neurogenic potential. The human SVZ is in close proximity to the nutrients and growth factors in the cerebrospinal fluid of the lateral ventricle from which it is separated only by the ependymal cell layer. The SVZ is enriched in proliferative compounds such as cannabinoids, neuropeptide Y, and growth factors and their receptors, all of which are important for the development and maintenance of multipotent stem cells in the adult brain.⁴

The hippocampus is a brain structure involved in the formation of memory and varied learning tasks; for

instance in rodents, the hippocampus is crucial for spatial memory and contextual discrimination. The hippocampus also harbours stem cells born in the SGZ, which lies immediately beneath the granule cell layer (GCL). The SGZ stem cells migrate into the GCL, differentiate and integrate into the host circuitry and become fully-functioning neurons. Extensive studies have been carried out on the GCL by labelling stem cells with viral vectors in order to follow the progression of a single cell and to determine which type of cell it differentiates into; recent studies have now shown that stem cells can grow to become fully functioning granular neurons.⁵

Stem cells are altered in neurological disorders

Neurodegenerative disorders alter the proliferation and neurogenic potential in the stem cell niche. In Huntington's disease there is a 2.8-fold increase in the number of proliferating cells in the SVZ, which includes increases in the three major classes of cells in the SVZ, namely neuroblast, glial/stem cells and transit amplifying cells. The degeneration of striatal neurons is the major driver of stem cell proliferation, although it still remains unclear as to whether SVZ stem cells migrate toward the striatum in the human brain. However, in the rodent brain, there is clear evidence for migration away from the SVZ toward the affected area with subsequent functional recovery after a Huntington-like lesion in the striatum.⁶ In stroke injury there is as much as a 30-fold increase in the numbers of proliferating cells in the SVZ in animal models and there is substantial migration toward the stroke lesion following occlusion of the middle cerebral artery.⁷ By contrast, in Parkinson's disease, the loss of the dopaminergic projections from the substantia nigra pars compacta leads to denervation of the dopaminergic input to the SVZ and as a result, one of the major proliferative cues is eliminated,⁸ resulting in a reduction in the number of proliferating stem cells in the SVZ. Primarily, the reduction in proliferation occurs due to reduced



Maurice A Curtis, PhD is a group leader and Lecturer in Anatomy at the University of Auckland. The main focus of his research is to determine how the human subventricular zone is affected by neurodegenerative disorders. Also, he works on aspects of neural progenitor cell migration in the normal and diseased brain.



Andrew S Naylor, PhD completed his PhD at Gothenburg University on the effects of running and enriched environment on adult neurogenesis. He is currently a post-doctoral research fellow at the University of Auckland, where he researches the effects of inflammation and infection on brain development.



Richard LM Faull, DSc is Professor of Anatomy at the University of Auckland and has had a long term research interest in neurodegenerative diseases of the human brain including Huntington's, Parkinson's, Alzheimer's disease and epilepsy. Over recent years he has had a major research interest in neurogenesis in human neurodegenerative diseases.

Correspondence to:
Dr Maurice A Curtis,
Email. m.curtis@auckland.ac.nz

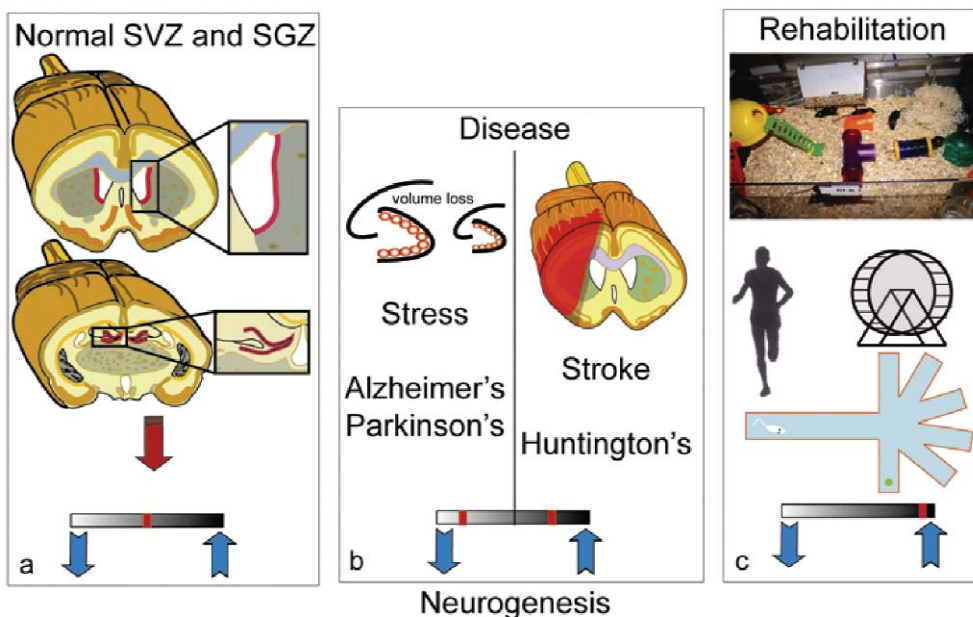


Figure Legend

a. Within the brain there are two stem cell germinal zones; the subventricular zone (SVZ, highlighted in red in the upper illustration) and the subgranular zone (SGZ, in red in the lower illustration). The level of neurogenesis from these germinal zones in the adult brain is moderate. However, b. under the conditions of stress, Alzheimer's or Parkinson's disease there is a reduction in the level of stem cells in the brain whereas in stroke and Huntington's disease there are increased numbers of stem cells. c. when laboratory animals and patients are exposed to an enriched environment and/or regular exercise, the stem cell proliferation is increased and the functional recovery after a brain insult is also improved.

dopamine signalling through the D2 receptors on proliferative cells.⁸ However, whether the lack of proliferation contributes to the symptomatology of Parkinson's disease is dubious due to the long distance from the substantia nigra to the SVZ. Stem cells are equally affected in Alzheimer's disease (AD) where the accumulation of toxic amyloid beta ($A\beta$) reduces the number of dividing cells; in addition, $A\beta$ promotes synaptic dysfunction and death of mature neurons in AD.⁹ Increased $A\beta$ production and depressed synaptic transmission in hippocampal slices¹⁰ suggest that $A\beta$ could participate in a negative feedback loop involved in synaptic modulation, since newly formed hippocampal neurons are sensitive to the intensity of synaptic transmission. The reports on stem cells in AD are conflicting, but in severe AD there is a reduction in stem cell production^{11,12} For more detailed review see Curtis et al.¹³

Stem cells in an enriched environment

Stem cells in the brain can be altered by exposing an individual to a range of enhanced external stimuli, such as social and physical / behavioural situations, hence, environmental enrichment. In this context, the key components of an enriched environment are in the novelty and complexity that these type of environments offer. These concepts have now moved forward towards a new and major focus; the enrichment of the environment in order to alter the characteristics of stem cells in the neurogenic niches. Environmental manipulations of the laboratory animal's habitat, using toys, ladders, tunnels, platforms and running wheels, significantly increases animal social interactions, improves learning and memory and promotes stem cell function in the SVZ and hippocampus.¹⁴ Furthermore, enrichment experiences lead to substantial neuron remodelling, with increased dendritic branching, synaptic plasticity (including long-term potentiation) and increased numbers of dendritic spines in cortical and hippocampal regions.

In enriched animals, stem cells are stimulated differentially in the discrete neurogenic compartments of the normal and damaged brain. Under normal conditions in the SVZ, no effect is generally seen on cell proliferation or neurogenic outcome after enrichment. However, environmental enrichment really comes to the fore after damage to the brain, with increased proliferation and neurogenesis seen after experimental stroke¹⁵ and in the enhancing effect that enrichment has on SVZ stem cell integration after stem cell transplantation in experimental stroke.¹⁶ Enriched environments may also play a large role in behavioural alterations in AD. In the hippocampus, enrichment increases proliferation and neurogenesis,¹⁷ increases neurotrophins, such as nerve growth factor (NGF) and brain derived neurotrophic factor (BDNF),¹⁸ mediates effects on angiogenesis and levels of vascular endothelial growth factor (VEGF),¹⁹ and plays a significant role in regulating and boosting cognition and improving spatial memory.

Stem cells respond to physical exercise

One of the major components of the enriched behavioural model for enhanced brain plasticity is the lab animal's free access to a running wheel. Physical exercise strongly and robustly induces hippocampal stem cell proliferation and neurogenesis.¹⁴ The effects of exercise-induced proliferation and neurogenesis is highly dependent on the neurotrophins BDNF and NGF, and the growth factors, insulin-like growth factor I (IGF-I) and levels of VEGF. Exercise also increases dendritic complexity and spine density in the hippocampus, increases angiogenesis and, importantly, significantly improves and enhances cognitive function and spatial memory. However, during periods of stress, increased levels of glucocorticoids significantly decrease hippocampal neurogenesis. The level of progenitor proliferation in running animals is decreased with excessive amounts of running activity. Together with increased levels

of glucocorticoids, hippocampal proliferation levels are highly dependent on the distance run and subsequent negative activation of the hypothalamic pituitary adrenal (HPA)-axis.²⁰ Given these findings, the magnitude of physical exercise should be carefully considered in devising enriched environment regimes.

However, challenges to the brain are well met by the stimulatory actions of exercise and may significantly involve changes in proliferation and neurogenesis. There is overwhelming evidence that regular exercise improves cognitive function in aged mice and elderly humans.²¹ In respect to AD, increased physical activity (walking, swimming and cycling) reduces the risk of cognitive decline. However, current preclinical models of AD suggest a greater effect on improved memory, increased neurogenesis and growth factor levels in animals exposed to the enriched environment compared to physical exercise. The enriched environment still demands greater physical activity and movement compared to more conventionally housed animals and this type of physically-linked behaviour may still play a strong role in enhancing brain function through stem cells.

Conclusion

The adult brain stem cell niches maintain the ability to respond to some neurodegenerative disorders throughout life. The SVZ and SGZ also have the ability to respond to external environmental changes that improve the plasticity of the adult brain. Whilst the virtues of lifelong regular physical exercise and enriching experiences on the prevention of various diseases and illnesses cannot be reiterated enough, adopting practices of healthy lifestyle with the right amount of physical activity and social interaction may prove to be vital for the appropriate rehabilitation of patients with neurological diseases. This focus will improve not only the motor but also the equally important sensory and social needs of the affected individuals.

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