Activation of Endogenous Stem Cells in the Brain –
A Novel Approach to Central Nervous System Disease  

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Abstract
Recent evidence from studies in rodents, primates and humans suggests that the formation of new brain cells from stem cells is part of the 'repertoire of plasticity' of the adult brain. Such plasticity offers a possible mechanism for functional flexibility through which the brain might also be induced to repair itself after injury or disease. New nerve cells are born when the brain is formed during embryonic and foetal development, and this process appears to continue throughout adulthood. Exogenously added molecules can regulate new cell formation and may thus provide a new therapeutic approach to tackle diseases of the brain and meet the growing medical need for the improved treatment of central nervous system disorders.

Keywords
Neurogenesis, stem cells, progenitors, central nervous system disease

Therapeutic Neurogenesis – New Biology
Meets a Growing Medical Need
The significant levels of unmet medical need, improved diagnostic techniques and growing awareness of central nervous system (CNS) disorders are likely to result in an enhanced focus on CNS therapeutics. The ageing population supports market growth, as age is probably the most significant non-genetic risk factor contributing to most CNS disorders, and the CNS disorders market is one of the largest and fastest-growing in the pharmaceutical industry. The current lack of drugs that cater to the increasing number of patients diagnosed with CNS disorders represents a significant challenge to the healthcare system and a great opportunity for the pharmaceutical industry.

New strategies to treat psychiatric and neurological disorders are called for where old ones have failed. Recent progress in our understanding of cell and tissue regeneration holds the promise of more effective treatments based on novel biology. However, are regenerative strategies applicable to the brain, which historically has been considered a static organ because of its highly organised and complex architecture? Today we know that underlying the functional flexibility of the CNS is a structural plasticity that is only beginning to be explored, and at the heart of this mechanism lies the stem cells of the adult brain.

Stem Cells and Neurogenesis in the Adult Brain
For a long time, the CNS seemed to be the most notable exception to the observation that tissues and organs in the body have an intrinsic ability to regenerate and self-repair. The founding father of modern neuroscience, Ramón y Cajal, stated in 1928 regarding the CNS that "everything may die, nothing may be regenerated". His view came to strongly influence the field for decades – not only the way experiments were performed, but also the way results were interpreted. However, subsequent studies1–5 have shown evidence for the formation of new neurons in the adult brain (adult neurogenesis). The scientific community was initially rather sceptical, but from having been a matter of scientific interest mainly to developmental biologists, the finding by Eriksson et al.4 that neurogenesis occurs in the adult human brain radically transformed the neurogenesis field. Exciting new avenues for research and prospects of new therapies for diseases of the brain have opened up, as we now view the adult brain as being capable of regeneration.

Two areas of the adult mammalian brain harbour stem/progenitor cells (aNSCs) and are capable of neurogenesis. Ependymal or astrocyte-like stem cells in the subventricular zone (SVZ) can give rise to new olfactory bulb neurons. In the dentate gyrus of the hippocampus, subgranular zone (SGZ) stem cells can proliferate and give rise to new mature granule cells.8 Stem cells divide symmetrically to give rise to two new stem cells, or asymmetrically to give rise to one stem cell and one progenitor cell. The multipotential progenitor cells divide further, migrate and differentiate into mature cellular phenotypes (neurons, astrocytes and oligodendrocytes). Beyond these two so-called neurogenic regions, the occurrence of neurogenesis is debated. There are indications of neurogenesis in the striatum, neocortex, amygdala, hypothalamus, piriform cortex and substantia nigra. It has been proposed that neurogenesis in these non-neurogenic areas could occur from resident progenitors and only...
Discovery

Stem Cells

if non-permissive conditions become permissive, e.g. following tissue damage, but currently available data are not conclusive. One source of conflicting views on how widespread neurogenesis is, may be found in the methodological limitations. Adult neurogenesis is a low-frequency event, and as such is difficult to study. The most common way to localise and quantify neurogenesis is to study the incorporation of bromodeoxyuridine (BrdU) or 3H-thymidine, both nucleotide analogues, which will also label cells undergoing DNA repair. The use of endogenous markers to identify newborn cells has been complicated by the fact that their expression can be upregulated under conditions other than neurogenesis. Other techniques include retroviral and transgenic labelling techniques and retrospective carbon-14 birth-dating of cells. Methods to enable the detection and quantification of aNSC in vivo in the human brain will prove important for the translation of the promising pre-clinical findings to clinically useful therapies.

Role and Regulation of Brain Regeneration

Neurogenesis is believed to play a major role in maintaining tissue homeostasis and optimal neurological function over time. It has been suggested that endogenous neurogenesis may play different roles in different parts of the healthy brain: maintenance and re-organisation of the whole system in the olfactory bulb, and modulation and refinement of existing neuronal circuits in the dentate gyrus. Best characterised are its specific roles in the normal brain in hippocampus-based learning and memory, as well as in olfactory function.

Neurogenesis is a dynamic process that is regulated by physiological factors. Limited access to oxygen or reduced calories are conditions that stimulate the production of new cells in the adult brain. Stress, on the other hand, is a state causing a reduction in neurogenesis. The positive effects of voluntary physical exercise on hippocampal neurogenesis in rodents have been well documented, and exposure to an enriched environment has been suggested to clinically useful therapies.

In Huntington’s disease (HD), the progressive neuronal degeneration is paralleled with an increase in SVZ neurogenesis in human post mortem material, correlating with the severity of disease. In patients suffering from Parkinson’s disease (PD), where dopamine-producing cells are selectively degenerated, aNSC proliferation in the SVZ is significantly reduced. Stimulating aNSC proliferation in pre-clinical models of PD results in a complete and lasting reversal of motor asymmetry. We can, at this time, only speculate on the exact role of the resulting new cells, whether proliferation results in an increased neurotrophic environment, which in turn revitalises remaining dopamine cell projections into the SVZ, or, alternatively, whether actual striatal/midg brain neurogenesis occurs. Taken together, the role of neurogenesis in these pathologies needs further clarification. Stroke-induced neurogenesis has been convincingly demonstrated not only in experimental models, but also in the adult human brain, even in elderly patients.

Neurogenesis and Disease

Exploiting the regenerative capacity of the brain to find new treatments for debilitating diseases such as neurodegenerative disease, stroke and depression is currently one of the most challenging and exciting prospects in medical research. Injury to the brain and disease will influence neurogenic activity in the adult brain, and both pre-clinical and clinical data show that neurogenesis is regulated in various human CNS disease states and in animal models thereof.

The role of stem cell activation in neurodegenerative disease presents a complex picture. Available data on neurogenesis in Alzheimer’s disease (AD) patients are contradictory, and the current status of our understanding could be summarised as follows: decreased proliferation is observed in post mortem material at early stages of disease, whereas proliferation is increased at later stages. The differing roles and extent of neurogenesis may indeed be dependent on the degree of permissibility of the micro-environment and, thus, correlate with the severity and/or stage of disease. It is also important to remember that AD is a heterogeneous disease with over 98% of cases being sporadic, which means that the molecular mechanisms vary between individual patients.

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Depression is probably the disease area where neurogenesis is most heavily implicated, albeit not yet understood from a mechanistic point of view. Neurogenesis clearly plays a role in mood regulation and in mediating the effects of antidepressants, but the exact nature of its involvement remains elusive. Apparently conflicting observations may be due to the choice of animal strains, behavioural tests or other technical discrepancies and further studies will be needed to clarify this.

Conclusion

Several mechanisms are part of the repertoire of plasticity that can contribute to regeneration of lost CNS function. In addition to
neurogenesis, mechanisms such as angiogenesis, sprouting, synchrony, neurotophism and neuroprotection can function to reduce the extent of damage or induce repair mechanisms, collectively improving neurological function. The therapeutic relevance of stimulating endogenous neurogenesis is currently one of the most promising and exciting new avenues to pursue for the development of new CNS therapies. Regenerative strategies towards treating CNS disease are already under way, and ongoing clinical studies will provide the first indications of the potential of this approach.
