Neural Stem Cells and the Aging Brain – Part II

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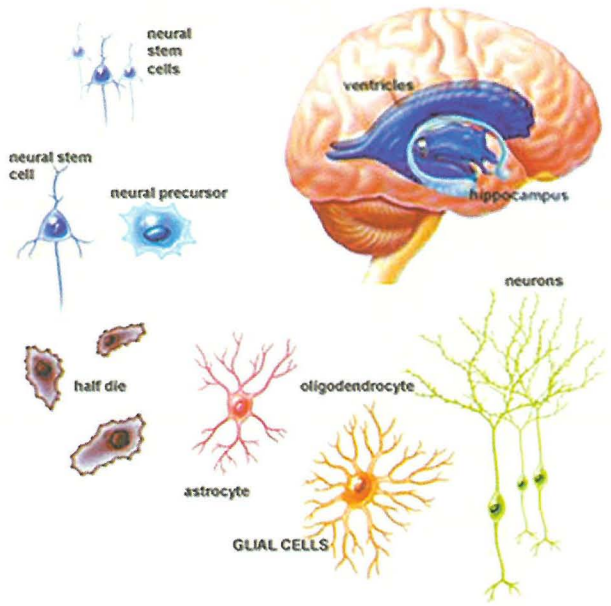
Neural Stem Cell Therapy

Neural stem cells have a number of potential applications in treating neurodegenerative disorders. Neurons lost during the disease process may be replaced either by facilitating the proliferation of neural stem cells already present in the brain (endogenous replacement) or else by transplantation of neural stem cells in the damaged area of the brain (exogenous replacement). For transplantation to be viable, cells have to fulfil three important criteria. Firstly, the transplanted cells must survive the procedure. Secondly, the transplanted neural stem cell has to develop in the required type of brain cell and finally, the transplanted cell must make the necessary connections to survive and be part of the existent neural network. If transplantation occurs in a diseased brain, the newly transplanted cell must also survive in the diseased environment. Although recent studies using animal models showed promising results, exogenous transplantation of neural stem cells is still a long way to go. One of the major limitations is that it is still difficult to produce the type of replacement cell needed following differentiation *in vivo*.



Transplant studies in humans have mostly used embryonic stem cells rather that neural stem cells. These have pluripotent characteristics giving them the ability to form all types of cells in the mature adult. However the use of stem cells having embryonic origin is highly controversial as it presents difficult moral and ethical issues. Moreover, success using this approach was limited especially in neurodegenerative disorders characterised by diffuse neuronal damage such as in Alzheimer's disease. The high oxidative stress coupled by the presence of the neurotoxic beta-amyloid protein also inhibits the survivability of transplanted stem cells.

A less invasive route would be the mobilisation of endogenous stem cells to replace the damaged ones. Indeed, there is substantial evidence indicating that neural stem cells are capable of responding to environmental cues that promote neurogenesis. Various studies show that neural stem cells are highly responsive to growth factors that affect the proliferation and survival of these cells. Such factors include the fibroblast growth factor and the epidermal growth factor, both of which have shown to act as activators of neural cell proliferation.[1] While treatment with growth factors can be regarded as a potential therapeutic approach, it is limited by the fact that neural stem cells will proliferate only to a certain number of cell divisions. Furthermore, neural stem cells in the aging brain exhibit decreased ability to proliferate under normal conditions and thus the ability of growth factors to stimulate cell proliferation may also be reduced in the aging brain.

Many factors regulate adult neurogenesis, and the issue of possible environmental influence on neural cell proliferation in the adult brain has been particularly investigated in the hippocampus because of its role in learning and memory processes and its involvement in Alzheimer's disease. Various research reports show that hippocampal-dependent learning, such as spatial memory formation, promotes neurogenesis in the hippocampus where the generation of new neurons is important in memory formation.[2] Animal models placed in an enriched environment including enhanced social interactions, show an increase in the number of hippocampal neurons. Similarly, increased exercise also showed increased hippocampal-associated neurogenesis possibly due to an increase in brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) mRNA in the hippocampus.[3,4] Interestingly, hippocampal neurogenesis is significantly inhibited in major depression, and anti-depressant therapies including drugs such as tricyclic antidepressants and selective serotonin/noradrenaline reuptake inhibitors and electroconvulsive therapy reverse it.[5] Whether this reduction in neural cell proliferation is directly correlated to changes in the mood pattern is still subject to further research.

The effects of social drugs such as alcohol and nicotine on adult neurogenesis have also been subject to extensive research. The effects of alcohol on the brain during development are well known especially during pregnancy – extensive use of alcohol results in foetal alcohol syndrome in which the brains of infants are significantly smaller in size then their normal counterparts. In fact, embryonic stem cells are highly sensitive to alcohol exposure, demonstrating increased apoptosis.

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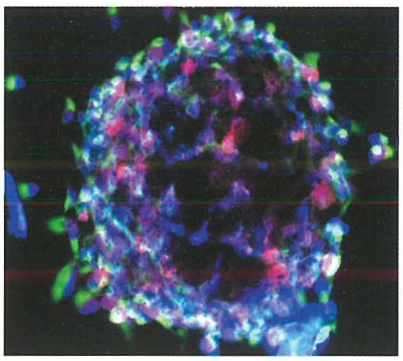
The effect of alcohol on adult brain neurogenesis is typically studied in the hippocampus, as hippocampal neurogenesis is believed to be essential in memory formation and chronic alcohol exposure leads to memory impairment. Rodent models of binge drinking have shown that chronic ethanol exposure prevents cell proliferation and survival of hippocampal neural stem cells.[6] Nicotine was also reported to impair neural cell proliferation in a dose-dependent manner. When rats were infused with nicotine for two weeks in a concentration normally found in adult heavy smokers, it was found that together with a significant reduction in cell proliferation in the hippocampus, spatial memory was also impaired.[7] Although more research is necessary to determine the cellular processes involved, these studies continue to highlight the harmful effects of alcohol and nicotine on the brain especially when neural cell proliferation is already compromised by old age or disease.

Changing the Cell Cycle

One approach that may be used to stimulate neural cell proliferation is to stimulate proteins that directly participate in cell division (cell cycle proteins). Potential targets are proteins known as telomeres and the enzyme that catalyses telomere lengthening, telomerase. Telomeres have long been recognised as being important in maintaining gene integrity by capping the ends of chromosomes and thus preventing DNA degradation.[8] However, telomere length also acts as a sort of a biological clock, regulating the number of cell divisions before the cell becomes inactive. Telomere length is maintained by the enzyme telomerase, which adds a short DNA sequence to the end of telomeres. The activity of this enzyme is maintained during adulthood in proliferating cells but is inactive in mature cells (cells that have differentiated completely). As aging progresses, telomere proteins become shorter thereby limiting the number of cell divisions to a finite number before permanent growth arrest. Therefore, changes in



telomere length and telomerase activity can drastically alter the lifespan of cells.

The rate of telomere shortening is sensitive to many factors and stressors that accompany old age. Of particular importance is oxidative stress which has been implicated in promoting the acceleration of telomere loss and reduced life span in a number of biological systems. Interestingly, shortened telomere length is now being linked to several age-related diseases which are believed to have oxidative stress as a causative factor, such as vascular dementia and atherosclerosis.[9] Oxidative stress has also been linked to Alzheimer's disease. Beta-amyloid protein, which is found in high quantities in the brains of these patients, is believed to act as a neurotoxic agent by causing oxidative stress in neurons leading to loss of neural cell proliferation in the hippocampus.[10]

Conclusion

Several strategies are currently being studied and developed in the hope of repairing damage associated with age-related neurodegenerative disorders. Among these, neural stem cells seem to offer a potential therapeutic strategy for some of the most devastating disorders which afflict the aging brain. As with any disease, the development of new therapeutic approaches relies heavily on extensive knowledge of the biological systems involved, and the ramification of alterations within the system following the onset of disease. Continued research is therefore necessary to fully understand the pathways critical for neural stem cell survival and differentiation and their significant role in the aging and diseased brain. This clearly represents one of the most important future challenges for basic and clinical neuroscientific research.

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