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CLINICAL IMPORTANCE OF NEUROGENESIS: AN OVERVIEW

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ABSRTACT

Neurogenesis, or the birth of new neuronal cells, was thought to occur only in developing organisms. However, recent research has demonstrated that neurogenesis does indeed continue into and throughout adult life in both vertebrate and invertebrate organisms. Examples of neurogenesis are found in the hippocampus of mammals, song control nuclei of birds and the olfactory pathway of rodents, insects and crustaceans. Ongoing neurogenesis is thought to be an important mechanism underlying neuronal plasticity, enabling organisms to adapt to environmental changes and influencing learning and memory throughout life. A number of different factors that regulate neurogenesis have been identified. Physical activity and environmental conditions have been known to affect proliferation and survival of neurons in vertebrates as well as invertebrates. It has been found that crayfish in an "enriched" environment had increased neurogenesis and neuronal survival compared to siblings in an "impoverished" environment. The neurogenesis may be defined as the process by which new nerve cells are generated. In neurogenesis, there is active production of new neurons, astrocytes, glia, and other neural lineages from undifferentiated neural progenitor or stem cells. Neurogenesis is considered a rather inactive process in most areas of the adult brain. This article presents a brief review of neurogenesis with an emphasis on it's clinically importance especially in human beings. Neurogenesis offers hope to individuals suffering from disorders including Parkinson's, Huntington's, and Alzheimer's disease; the article also reveals the concept of adult neurogenesis as well as regulation of neurogenesis.

KEY WORDS: Neurogenesis, Neuroscience, Neurotransmitters, Neuronal cells.

INTRODUCTION

Neurogenesis (birth of neurons) is the process by which neurons are generated. Most active during pre-natal development, neurogenesis is responsible for populating the growing brain. Throughout history, neuroscientists have commonly believed that once the brain is damaged, there is no way to repair it. However, in the past few years, scientists have discovered that the brain does change throughout life, and can possibly repair itself as well as be enhanced by healthy activities including exercise and proper nutrition. Neurogenesis offers hope to individuals suffering from disorders including Parkinson's, Huntington's, and Alzheimer's disease. One of the main goals of researchers is to develop drugs to stimulate areas of the brain to repair itself by replacing its own cells (Gage, 2003). In the 1960's and 1970's, researchers discovered that some parts of the adult brain can repair itself. A number of studies during this time found that the axons of the neurons in the brain and spinal cord can regrow to some degree after trauma. More recently, in 1998, Eriksson and colleagues studied post-mortem human brain tissue and found that new neurons were generated in the human hippocampus, an area of the brain that helps regulate memory and learning (Eriksson *et al.*, 1998). Researchers have also found that neurogenesis occurs in adult mice, birds, and other primates.

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The brain is made of billions of nerve cells and makes up approximately 2% of the total body weight. Yet, it is a demanding organ that uses up to 30% of the day's calories and nutrients. If the brain receives improper or insufficient amounts of key nutrients from our daily diet, serious issues can develop with the neurotransmitters and our health in general. In addition to poor eating habits, stress and trauma from any source, worry, illness, surgery, the use of any external chemical and even pollution can alter or deplete neurotransmitters. Nutritional supplementation is often the best way for our body and brain to receive the needed nutrition and neuroscience shows us that amino acids can serve as precursors to these neurotransmitters. Neurogenesis has made understanding neuroscience its primary focus. This understanding of neuroscience and the effect amino acids have on neurotransmitters has given neurogenesis the knowledge to formulate products that can support healthy brain function. Neurogenesis nutritional supplements are formulations of vitamins, minerals and amino acids that are designed to target the effected neurotransmitters and assist the brain in balancing and rebuilding these neurotransmitters to achieve and maintain a chemical balance. This chemical rebuilding process of neurotransmitters has brought relief and freedom to thousands.

CONCEPT OF ADULT NEUROGENESIS

Adult neurogenesis is the process of generating new neurons which integrate into existing circuits after fetal and early postnatal development has ceased. In most mammalian species, adult neurogenesis only appears to occur in the olfactory bulb and the hippocampus. In addition there is a high level of adult neurogenesis in the olfactory epithelium (considered part of the peripheral nervous system) where olfactory receptor neurons are constantly replaced. The process appears more widespread but still limited in other vertebrate classes, having been described in select brain regions of certain birds, fish and reptiles.

Furthermore, many invertebrates and vertebrates have neural regenerative capacities that involve neurogenesis (such as tail regeneration in salamanders). New neurons are continually born throughout adulthood in predominantly two regions of the brain:

►The subventricular zone (SVZ) lining the lateral ventricles, where the new cells migrate to the olfactory bulb via the rostral migratory stream.

►The sub granular zone (SGZ), part of the dentate gyrus of hippocampus.

Many of the newborn cells die shortly after they are born, but a number of them become functionally integrated into the surrounding brain tissue. Adult neurogenesis is a recent example of a long-held scientific theory being overturned, with the first evidence of mammalian neurogenesis presented in 1992 (Reynolds and Weiss, 1992). Early neuroanatomists, including Santiago Ramon y Cajal, considered the nervous system fixed and incapable of regeneration. In 1983, with the characterization of neurogenesis in birds (Goldman and Nottebohm,1998) and the use of confocal microscopy, the possibility of mammalian neurogenesis became more apparent, but it was not until the early 1990s that hippocampal neurogenesis was demonstrated in non-human primates and humans (Eriksson *et al*., 1998 and Gould *et al.*, 1999). More recently, neurogenesis in the cerebellum of adult rabbits has also been characterized (Ponti *et al*., 2008).

CLINICAL IMPORTANCE OF NEUROGENESIS

Neurogenesis and learning

The functional relevance of adult neurogenesis is uncertain (Kempermann *et al.*, 2004). But there is some evidence that hippocampal adult neurogenesis is important for learning and memory (G Neves *et al.*, 2008). Multiple mechanisms for the relationship between increased neurogenesis and improved cognition have been suggested, including computational theories to demonstrate that new neurons increase memory capacity (Becker, 2005), reduce interference between memories (Wiskott *et al.*, 2006), or add information about time to memories (Aimone *et al*., 2006) . Experiments aimed at ablating neurogenesis have proven inconclusive, but several studies have proposed neurogenic-dependence in some types of learning (Shors *et al*., 2002). and others see no effect. Studies have demonstrated that the act of learning itself is associated with increased neuronal survival. However, the overall findings that adult neurogenesis is important for any kind of learning are equivocal.

Neurogenesis and stress

Adult-born neurons appear to have a role in the regulation of stress. Studies have linked neurogenesis to the beneficial actions of specific antidepressants, suggesting a connection between decreased hippocampal neurogenesis and depression (Malberg *et al*., 2000 and Manev *et al*., 2001).

In a subsequent paper, scientists demonstrated that the behavioural benefit of antidepressant administration in mice is reversed when neurogenesis is prevented with x-irradiation techniques. Some studies have hypothesized that learning and memory are linked to depression, and that neurogenesis may promote neuroplasticity. One study proposes that mood may be regulated, at a base level, by plasticity, and thus *not chemistry*. Accordingly, the effects of antidepressant treatment would only be secondary to change in plasticity (Castrén, 2005).

Effect of sleep reduction and stress levels on neurogenesis

One study has linked lack of sleep to a reduction in rodent hippocampal neurogenesis. The proposed mechanism for the observed decrease was increased levels of glucocorticoids. It was shown that two weeks of sleep deprivation acted as a neurogenesis-inhibitor, which was reversed after return of normal sleep and even shifted to a temporary increase in normal cell proliferation (Mirescu *et al*., 2006).

Neurogenesis and Parkinson's disease

Parkinson's disease is a chronic and neurodegenerative disorder characterized by a progressive loss of dopaminergic neurons in the nigrostriatal projection. Parkinson's disease (also known as Parkinson's, Parkinson disease or PD) is a degenerative disorder of the central nervous system that often impairs the sufferer's motor skills, speech, and other functions. Parkinson's disease belongs to a group of conditions called movement disorders. It is characterized by muscle rigidity, tremor, a slowing of physical movement (bradykinesia) and a loss of physical movement (akinesia) in extreme cases (Jankovic, 2008).

Parkinson's disease occurs when the neurons that are located in the brain stem's substantia nigra are destroyed. These neurons work by connecting with other neurons in the corpus striatum, which then send messages to the areas in the cortex which control motor functioning. Parkinson's patients have a decreased number of neurons in the substantia nigra, which causes a decrease in the amount of dopamine in the brain. This results in a decrease in the number of signals that are sent to the corpus striatum, which interferes with the normal functioning of the nervous system. (Arenas, 2002). Current approaches for the treatment of Parkinson's disease include treating the symptoms of the disease with a combination of L-DOPA and carbidopa, which will increase the synthesis and release of dopamine. These medications are effective in the early stages at alleviating symptoms of tremor and stiffness and slowness of movement. A drawback of this treatment is side effects such as nausea, vomiting and hypertension. As the disease progresses, less dopamine neurons are available to synthesize dopamine and the effectiveness of the treatment decreases. Other approaches that can be used are deep brain stimulation and fetal tissue transplantation. Deep brain stimulation uses stimulating electrodes to control tremors. Fetal tissue transplantation involves transplanting human embryonic brain tissue into patients. The hope with this treatment is that the neural stem cells will develop and produce dopamine in the patient.

Transplantation of fetal dopaminergic precursor cells has paved the way for the possibility of a cell replacement therapy that could ameliorate clinical symptoms in affected patients (Arias-Carrión *et al*., 2007).

Recent years have provided evidence for the existence of neural stem cells with the potential to produce new neurons, particularly of a dopaminergic phenotype, in the adult mammalian brain. Neural stem cells have been identified in the neurogenic brain regions, where neurogenesis is constitutively ongoing, but also in the non-neurogenic zones, such as the midbrain and the striatum, where neurogenesis is not thought to occur under normal physiological conditions. A detailed understanding of the factors governing adult neural stem cells *in vivo* may ultimately lead to elegant cell therapies for neurodegenerative disorders such as Parkinson's disease by mobilizing autologous endogenous neural stem cells to replace degenerated neurons (Fallon *et al*., 2000).

Neurogenesis and exercise

Scientists have shown that physical activity in the form of voluntary exercise results in an increase in the number of newborn neurons in the hippocampus of aging mice. The same study demonstrates an enhancement in learning of the "runner" (physically active) mice (Van *et al*., 2005). While the association between exercise-mediated neurogenesis and enhancement of learning remains unclear, this study clearly demonstrates the benefits of physical activity and could have strong implications in the fields of aging and/or Alzheimer's disease.

Neurogenesis and old age/Alzheimer's disease

Neurogenesis could also be useful in the treatment of Alzheimer's disease. Alzheimer Disease is a progressive neurodegenerative disease that causes death of nerve cells in the brain. The symptoms include loss of memory and reasoning as well as personality and behavioural changes (Berchtold and Cotman, 1998). Studies have been conducted on mice focusing on the gene Presenilin-1 (PSI), which is found in both mice and humans. Mutations in this gene are often found in humans that have early onset Alzheimer's. PSI works by encoding a protein in brain cells located in the hippocampus and other brain regions that control memory and learning. Joe Tsien and colleagues deleted PSI from the mouse brains, and then put the mice into an environment where they were subjected to a number of tests to aid memory and learning. They found that the mice that had the PSI gene deleted formed less nerve cells after being in a stimulating environment, which suggests that PSI is a major factor in neurogenesis. The mice without PSI seemed to recall more information at first, but had problems clearing out memories copied in the cortex. Tsien suggested that the mice's brains may become "overloaded" and therefore it will become difficult for the mice to form long-term memories. This shows a similarity to the problems that

Alzheimer's sufferers face, since in the early stages of the disease people have difficulty forming long-term memories. These findings may also help to explain the problems that researchers have had with insertion of stem cells, since it is possible that the new neurons could erase memories.

Allopregnanolone, a neurosteroid aids the continued neurogenesis in the brain. Levels of allopregnanolone in the brain decline in old age and Alzheimer's disease (Marx *et al*., 2006). Allopregnanolone has been shown through reversing impairment of neurogenesis to reverse the cognitive deficits in a mouse model of Alzheimer's disease (Wang *et al*., 2010).

Neurogenesis and Huntington's disease

Huntington's disease, chorea, or disorder (HD), is a progressive neurodegenerative genetic disorder, which affects muscle coordination and leads to cognitive decline and dementia. It typically becomes noticeable in middle age. HD is the most common genetic cause of abnormal involuntary writhing movements called chorea and is much more common in people of Western European descent than in those from Asia or Africa. The disease is caused by an autosomal dominant mutation on either of an individual's two copies of a gene called Huntingtin, which means any child of an affected parent has a 50% risk of inheriting the disease (Walker, 2007) . There is no treatment currently available that can halt the devastating effects of Huntington's disease. However, there are medications that can be taken to help treat emotional and movement problems. Antipsychotic drugs can be used to help control symptoms including hallucinations and delusions. These medications have the unwanted effect of causing further stiffness in patients suffering from muscle contractions called dystonia. For depressive symptoms, selective seretonin reuptake inhibitors can be prescribed. Tranquilizers are often used to control anxiety, and mood stabilizers can be prescribed to control mood swings.

Research is currently being done in many different areas in an effort to find a cure for the disease. One area of research includes fetal tissue and stem cell studies that attempt to restore neurons in the brain. Imaging techniques such as magnetic resonance imaging (MRI) have also been used to measure increases or decreases in brain chemicals thought to play a role in the disease, so that researchers can gain a better understanding of how Huntington's disease leads to neuron death. A recent study conducted by Curtis and colleagues used post-mortem brain tissue from Huntington's disease patients in order to examine whether neurogenesis occurs in the SEL region located beside the caudate nucleus in the brain where cell death has occurred. The results of this study showed that neurogenesis occurred in these areas, showing that the brain has the ability to repair itself. The researchers are not clear which factors caused the growth of the cells, and the increase was not large enough to compensate for the high levels of cell death in Huntington's patients. The hope is that the level of cell growth could be increased through growth factors or pharmaceuticals, to develop an effective treatment for neurological disease (Curtis *et al*., 2003)

Regulation of Neurogenesis

Many factors may affect the rate of hippocampal neurogenesis. Exercise and an enriched environment have been shown to promote the survival of neurons and successful integration newborn cells into the existing hippocampus (Van *et al*., 2005). Another factor is central nervous system injury since neurogenesis occurs after cerebral ischemia, epileptic seizures, and bacterial. On the other hand, conditions such as chronic stress and aging can result in a decreased neuronal proliferation (Lee *et al*., 2002 and Sheline *et al*., 2003).

CONCLUSION

It may be concluded that neurogenesis is the process by which new nerve cells are generated; neurogenesis is thought to be an important mechanism underlying neuronal plasticity, enabling organisms to adapt to environmental changes and influencing learning and memory throughout life. Neurogenesis offers hope to individuals suffering from various neurodegenerative disorders including Parkinson's, Huntington's, and Alzheimer's disease. One of the main goals of researchers is to develop drugs to stimulate areas of the brain to repair itself by replacing its own cells. Neurogenesis is regulated by growth factors that can lead to the development of new cells. Once the cells become either glial cells or neurons, other growth factors including brain-derived neurotrophic factor keep the cells alive. New neurons in the human brain have been found in the ventricles of the forebrain as well as the hippocampus. The cells that become neurons travel to the olfactory bulbs.

Researchers have speculated that neurogenesis occurs in the hippocampus since this area is so important in memory and learning. Other researchers have attempted to discover if neurogenesis occurs in other areas of the brain and spinal cord, but have not yet found conclusive evidence to support this hypothesis. It is anticipated that new techniques will be able to direct neurogenesis in other areas of the brain. Uses of this technique would include enabling the brain to repair damage and to enhance mental functioning. There are a number of concerns that researchers will need to address once neurogenesis-enabling treatments become available. Among these include:

►Possible modification of a person's central nervous system.

►Moral issues concerning the source of stem cells (embryos).

►Future possibility of over-population (as a result of life extension).

►Safety of procedures

►Ensuring all humanity benefits from these treatments (including developing countries and non-technocratic elite).

►Informed consent in cases where the individual's disease is in an advanced stage.

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