Neurogenesis and Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is a neurodegenerative disease, characterized in the brain by amyloid plaque deposits and neurofibrillary tangles. It is the most common form of dementia among older people. There is at present no cure for AD, and current treatments consist mainly in drug therapy. Potential therapies for AD involve gene and cellular therapy. The recent confirmation that neurogenesis occurs in the adult brain and neural stem cells (NSCs) reside in the adult central nervous system (CNS) provide new opportunities for cellular therapy in the CNS, particularly for AD, and to better understand brain physiopathology. Hence, researchers have aimed at characterizing neurogenesis in patients with AD. Studies show that neurogenesis is increased in these patients, and in animal models of AD. The effect of drugs used to treat AD on neurogenesis is currently being investigated, to identify whether neurogenesis contributes to their therapeutic activities.

Keywords: neural stem cells, hippocampus, learning and memory, acetylcholinesterase inhibitors, N-methyl-D-aspartate-glutamate receptor antagonist, cellular therapy.

Introduction

The recent confirmation that neurogenesis occurs in the adult brain and NSCs reside in the adult CNS in various species including humans, is as important for cellular therapy in the CNS, particularly for neurodegenerative diseases like AD, as for our understanding of developmental biology (Gage, 2000; Taupin and Gage, 2002). Environmental enrichment, drugs, trophic factors, neurotransmitters, and a broad range of physiopathological conditions, including AD, modulate adult neurogenesis (Taupin, 2005). Recently, using a combination of mouse models and X-irradiation, to inhibit neurogenesis, it was reported that antidepressants, like fluoxetine, increase hippocampal neurogenesis, which contribute to their behavioral effects (Santarelli et al. 2003). Researchers have aimed to investigate whether neurogenesis may contribute to the therapeutic effects of drugs used to treat other neurological diseases and disorders, particularly AD (Jin et al. 2006).

Alzheimer's disease is associated with the loss of nerve cells in areas of the brain that are vital to memory and other mental abilities, like the hippocampus (Hardy and Selkoe, 2002; St George-Hyslop and Petit, 2005). Hence, cognitive impairments that worsen overtime are major disabilities of AD. Two classes of drugs are currently used to treat patients with AD: acetylcholinesterase (AChE) inhibitors, like tacrine, donepezil, galantamine and rivastigmine, and an N-methyl-D-aspartate (NMDA)-glutamate receptor antagonist, like memantine (Arrieta et al. 1998; Scarpini et al. 2003; Wilkinson et al. 2004; McShane et al. 2006). These drugs produce improvements in cognitive and behavioral symptoms, but their role in the pathogenesis of AD is unknown. AChE inhibitors are thought to improve cognitive functions by enhancing cholinergic neurotransmission in affected brain regions of AD.

Neurogenesis in Alzheimer's Disease

Jin et al. (2004) studied neurogenesis from autopsies of AD brain patients. The expression of markers for immature neuronal cells, doublecortin, polysialylated nerve cell adhesion molecule and neurogenic differentiation factor, increase in the subgranular zone (SGZ), granular layer of the dentate gyrus (DG), and CA1 region of hippocampal Ammon's horn (Jin et al. 2004a). The SGZ is a layer beneath the granular layer. Newly generated neuronal cells in the SGZ migrate to the granular layer where they differentiate into neuronal cells of the DG (Taupin and Gage, 2002). Studies also show that neurogenesis is modulated in animal models of AD. Animal models have been devised to study genes involved in AD, like presenilin 1 (PSEN1) and amyloid-beta protein precursor (APP) (German and Eisch, 2004).

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PSEN1 and APP are associated with most cases of early-onset AD, a rare hereditary form of dementia (St George-Hyslop and Petit, 2005). Neurogenesis is positively regulated in the DG of transgenic mice that express the Swedish and Indiana APP mutations, a mutant form of human APP (Jin et al. 2004b), and negatively regulated in the DG and subventricular zone (SVZ) of knock-out mice for PSEN1 and APP (Feng et al. 2001; Wen et al. 2002). The DG and SVZ are the two main regions of the CNS where neurogenesis occurs in the adult (Taupin and Gage, 2002). These animal studies were performed using bromodeoxyurine (BrdU) labeling, a thymidine analog that incorporates into the DNA of dividing cells during the S-phase of the cell cycle, and is used for birthdating cells and monitoring cell proliferation (Miller and Nowakowski, 1988; Taupin and Gage, 2002). The discrepancies between the studies could be explained by the limitation of the transgenic animal models as representative of complex diseases, and to study adult phenotypes, like adult neurogenesis (Dodart et al. 2002). Particularly, mutant or deficient mice for single genes, like PSEN1 and APP, may not fully reproduce the features of AD, associated with loss of multiple cell types.

Four to 10% of nerve cells in regions in which degeneration occurs in AD, like the hippocampus, are tetraploids (Yang et al. 2001). Nerve cells may have entered the cell cycle and underwent DNA replication, but did not complete the cell cycle. It is proposed that cell cycle re-entry and DNA duplication precedes neuronal death in degenerating regions of the CNS (Herrup et al. 2004). As BrdU incorporates DNA of dividing cells during the S-phase of the cell cycle, BrdU labeling will not allow to discriminate cell proliferation versus cell cycle re-entry and DNA duplication without cell division. The existence of aneuploid cells may account for some of the newly generated neuronal cells observed using BrdU-labeling in experimental models of AD. Therefore, though reports suggest that neurogenesis is enhanced in AD. This remains to be further confirmed in the light of recent data showing the existence of tetraploid cells in regions in which degeneration occurs in AD.

Effect of Drugs Used to Treat AD on Neurogenesis

Researchers have aimed to identify the effect of drugs used to treat AD on neurogenesis. The effects of tacrine, galantamine and memantine on neurogenesis were assessed in adult mice, using the BrdU-labeling paradigm (Jin et al. 2006). The three drugs increase neurogenesis in the DG and SVZ by 26–45%, except tacrine that does not alter BrdU labeling in the DG. These results show that drugs used to treat AD increase neurogenesis in the adult brain, which may contribute to their therapeutic effects (Jin et al. 2006). Neurogenesis is enhanced in AD (Jin et al. 2004), and drugs used to treat AD also increase neurogenesis. The function of increased neurogenesis in AD brain, and by drugs used to treat AD remain to be elucidated. Some speculations can be raised. The increase neurogenesis in AD may represent a regenerative attempt by the CNS, to compensate for the loss of nerve cells. It may also represent a compensatory process to increase CNS plasticity in the diseased brain (Taupin, 2006). One can speculate that drugs used to treat AD would then attempt to amplify such processes. The mechanism of action of these drugs on neurogenesis remains to be elucidated, as well. Lesion of the cholinergic forebrain impairs hippocampal neurogenesis in adult rats and muscarinic receptors have been identified on newly generated neuronal cells in the SGZ and SVZ. This suggests that the cholinergic pathway promotes neurogenesis (Cooper-Kuhn et al. 2004; Mohapel et al. 2005). Since AChE inhibitors are thought to improve cognitive function by enhancing cholinergic neurotransmission in affected brain regions of AD and, tacrine, galantamine may promote neurogenesis through a similar mechanism. The reason why tacrine that do not alter BrdU labeling in the DG remains to be further investigated. NMDA receptor antagonists on the one hand promote neurodegeneration (Ikonomidou et al. 1999). On the other hand, they promote neurogenesis in the adult brain (Cameron et al. 1995, 1998; Gould et al. 1997; Nacher et al. 2001, 2003). Therefore, the therapeutic effect of memantine, an NMDA-glutamate receptor antagonist, in AD may also be mediated through stimulation of neurogenesis. These hypotheses and the mechanisms of action of drugs used for the treatment of AD remain to be confirmed, and investigated.

Stem Cell Therapy for the Treatment of AD

Because AD is associated with the loss of nerve cells, cellular therapy is considered for the

treatment of this disease. With the recent evidence that neurogenesis occurs in the adult brain and NSCs reside in the adult CNS, new strategies for the treatment of neurodegenerative diseases, and particularly AD, are being considered and are promising: the transplantation of adult-derived neural progenitor and stem cells, and the stimulation of endogenous neural progenitor cells. Experimental studies reveal that adult derived-neural progenitor and stem cells engraft the host tissues (Gage et al. 1995; Shihabuddin et al. 2000), and promote functional recovery in animal models of neurodegenerative diseases, like multiple sclerosis (Pluchino et al. 2003). In AD, like multiple sclerosis, the degeneration is widespread, therefore direct transplantation of neural progenitor and stem cells in the brain may not offer an optimum strategy for treating these diseases. Neural progenitor and stem cell migrate to diseased and injured sites in the brain, when administered by systemic injection (Macklis et al. 1993; Pluchino et al. 2003; Fujiwara et al. 2004). Such ways of delivering neural progenitor and stem cells, that are also non-invasive, may prove to be valuable for the treatment of AD. Neurogenesis is enhanced in the diseased brain, particularly in AD (Jin et al. 2004a). This suggests that the brain has the potential to self-repair, and that endogenous progenitor cells may be recruited to replace degenerated nerve cells and promote functional recovery. Future studies will aim at identifying factors that promote neurogeneis in AD, as candidates for cellular therapy.

Conclusion

Neurogenesis is enhanced in AD, and drugs used to treat AD, though acting through different mechanisms of action, increase neurogenesis. This may contribute to their therapeutic effects. Santarelli et al. (2003) reported using a combination of mouse models and X-irradiation -to inhibit neurogenesis-, that antidepressants, like fluoxetine, increase hippocampal neurogenesis, which contribute to their behavioral activities. Meshi et al. (2006), using the same approaches, reported that neurogenesis does not mediate the behavioral effects of environmental enrichment (Meshi et al. 2006). Inhibition of neurogenesis is therefore key to determine causal relationship between neurogenesis and a physiological or pathological function. Therefore, it remains to evaluate the consequence of inhibiting neurogenesis on the effect of drugs used for the treatment of AD, to establish a causal relationship between their therapeutic effects and the stimulation of neurogenesis. Nonetheless, the evidence that drugs used to treat AD positively regulate neurogenesis may lead to new drugs design, and new strategies to treat AD. To this aim, unraveling the cellular and molecular mechanisms of action of drugs to treat AD, on neurogenesis, will be a key factor.

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