The New Approach in Development of Anti-Alzheimers Disease Drugs via the Cholinergic Hypothesis and Amyloid Hypothesis

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Enhancing the activity of cholinergic neurons has been regarded as one of the most promising methods for Alzheimers disease (AD) treatment. Recently, acetylcholinesterase inhibitors (AChEIs) have been studied for other mechanisms of action, such as neuroprotective action and lowering of $\beta$-amyloid. Greig, et al. has published that butyrylcholinesterase inhibitors reduced $\beta$-amyloid plaque in in vivo study. However, the amyloid hypothesis is believed to be the most promising approach in the development of anti-AD drugs. There are several approaches to AD drug development using the amyloid hypothesis. Among these approaches are (1) $\alpha$ -secretase enhancer, (2) $\beta$ -secretase inhibitor, (3) $\gamma$ -secretase inhibitor and (4) anti-aggregation of $\beta$ -amyloid plaque. All of these approaches, however, have shown certain weak points but some pharmaceutical companies have managed to overcome these weak points at the least in their preclinical study. And some pharmaceutical companies may put into practice their methods in the clinical stage now. I will discuss The New Approach in Development of anti-Alzheimers Disease Drugs via the Cholinergic Hypothesis and Amyloid Hypothesis

Clinical aspects of Alzheimer's disease: Current status and issues to have to be solved.

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It is well known that Alzheimer's disease (AD) is the most common etiology of age-associated dementia in the world including Japan. The long-term care insurance started in 2000 has made the issues of dementia more visible in the community than before. However, many issues still remain to be solved from the clinical point of view. One of the most serious problems is the underdiagnosis of persons with dementia in the community. It is estimated that the number of persons with dementia is approximately 2 million. It is not known at all how many of them are being diagnosed and appropriately managed in the community. It is well recognized that early pharmacotherapy with antidementia drugs is essential in the clinical management of persons with AD. Thus, the underrecognition of dementia is closely related to the subsequent issues including pharmacotherapy to behavioral complications with antipsychotics by off-label use, the treatment of demented persons with physical complications, etc. Also, an legal issue which is closely related to the management of persons with dementia is how to obtain medical informed consent from them. The future strategies will be discussed from the clinical point of view.

Novel therapeutic strategy for neurogenesis in the neurodegenerative disorders

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Promotion of neurogenesis is a potential therapeutic strategy for neurodegenerative disorders such as Alzheimer's disease and stroke. We here introduce useful drugs to improve the stroke-induced deficits of cognitive function through promotion of neurogenesis. Sodium orthovanadate treatment enhances proliferation of progenitor cells in the adult rat SVZ after focal cerebral ischemia. The promotion of neurogenesis is associated with increased activities of Akt and ERK in the SVZ. Preliminary in vivo data indicate that peripheral administration of a vanadium compound 7 days after focal cerebral ischemia in mice significantly increased neurogenesis in the SGZ of dentate gyrus. The vanadium compound-induced proliferation is blocked by inhibitors of Akt and ERK pathways consistent with the finding that the treatment induces increase in Akt and ERK activities in neurons of the SGZ. Interestingly, the increased neurogenesis is associated with improvement of spatial reference memory and cognitive function. Taken together, the in vivo neurogenic properties of vanadium compound with easy penetration into the brain and lack of toxicity strongly suggest a novel therapeutic strategy for neurogenesis in the neurodegenerative disorders such as Alzheimer's disease.

Treatment of Alzheimer Disease - Status Quo and Future Considerations

Shun Shimohama


Numerous approaches have been explored to treat individuals with Alzheimer disease (AD). General approaches include the following: treatment of secondary symptoms, treatment of cognitive symptoms, slowing decline, delaying onset of disease, and primary prevention. While in the past many of our attempts have been to treat secondary symptoms or improve the cognitive deficits, future attempts are likely to focus on slowing the rate of decline, delaying the onset of appearance, or preventing the disease. New design trials will be necessary to address these issues, including longer trials designed to examine the effects of drugs on slope changes over time. In addition, procedures will need to be developed to distinguish relatively brief symptomatic improvement from an underlying changes in brain structure. As the design of our clinical trials becomes more focused on slowing or preventing further progression, they will become increasingly complex and lengthy. In the future, the issue of pharmacoeconomics is likely to play an increasing role in decisions regarding reimbursement for drugs. Future clinical drug trials are likely to regard the areas of ADLs, quality of life, and pharmacoeconomics as increasing important outcome measures.