Institutionen för neurobiologi, vårdvetenskap och samhälle
Alzheimer neurobiologi center

Stimulating Neuroprotective and Regenerative Mechanisms in Alzheimer Disease

AKADEMISK AVHANDLING
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ABSTRACT

The processes involved in neuroprotection and brain repair are an important aspect of the preservation and restoration of neuronal functions affected by pathological lesions. Mechanisms that stimulate, manage and regulate these processes thus hold potential for the development of treatment strategies for Alzheimer disease (AD). The aim of this thesis was to increase our understanding of the stimulation of neuroprotective and regenerative mechanisms, in particular with respect to amyloid-β (Aβ) accumulation and other pathological processes associated with AD.

Mounting evidence suggests that the continuous loss of cholinergic neurons and nicotinic receptors (nAChRs) in the hippocampus and cerebral cortex could be mediated through an interaction between α7 nAChRs and Aβ species. In ***paper I***, we investigated interaction of α7 nAChRs with different forms of Aβ, and the functional consequences of these interactions. We found that α7 nAChRs play an important role in mediating neuroprotective actions against Aβ-induced neurotoxicity, and that the assembly form of Aβ is important for the interaction with α7 nAChRs and the downstream effects in neuronal cells. Fibrillar Aβ appears to cause cytotoxic effects by blocking α7 nAChRs, whereas oligomeric Aβ seems to activate α7 nAChRs to modulate calcium-dependent synaptic function.

In ***paper II***, we characterized the neuroprotective and neurotrophic actions of amyloid-modulatory candidate drugs (–)- and (+)-phenserine and its primary metabolites, and investigated the primary signaling pathways responsible for mediating these effects. (+)-Phenserine increased the proliferation of mouse neural progenitor cells in culture via activation of MAPK signaling pathways, including elevated cortical levels of brain-derived neurotrophic factor in mouse brain. In ***paper III***, we investigated the modulating effects of (+)-phenserine on the changes in brain synaptic function, hippocampal neurogenesis, and inflammatory cells at different stages of amyloid pathology. (+)-Phenserine increased proliferation of neural progenitor cells, and increased the maturation of newborn neurons in the hippocampi of young adult Tg2576 mice but not in older mice with advanced Aβ plaque pathology.

In ***paper IV***, we investigated the effects of stem cell transplantation and modulation of Aβ and α7 nAChRs on endogenous neurogenesis and astrocytosis, graft survival, and cognition. Intrahippocampi transplantation of human neural stem cells (hNSCs) improved spatial memory in young adult Tg2576 mice, and increased endogenous hippocampal neurogenesis. (+)-Phenserine increased graft survival but blocked the hNSC transplant-mediated increase in endogenous neurogenesis, indicative of interfering mechanisms of action. We found that α7 nAChR-expressing astrocytes accumulated along the needle track after transplantation, and that the numbers of these astrocytes correlated with the degree of endogenous hippocampal neurogenesis. Hence, we postulate a hitherto unexplored role for α7 nAChR-expressing astrocytes in neurogenesis and tissue remodeling.

The clinical implications of stimulation of neuroprotection and brain repair in the course of AD are currently under investigation. However, it is my hope that the cumulative findings presented in this thesis will provide a better understanding of the possibilities and limitations of these therapeutic strategies that aim to change or halt the clinical progression of AD.

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