Endocrine regulation of Alzheimer’s disease. The Achilles heel of dementia and other neurological conditions

Alzheimer’s disease (AD) is the most common disorder of the central nervous system and the most frequent cause of devastating dementia in the elderly. Typified by loss of memory and by cognitive decline, AD lowers the quality of life of patients, puts a major burden on the family and costs countries around the world billions of dollars annually. Because people are living longer, the number of individuals affected by Alzheimer’s disease is continuing to increase, thereby augmenting world-wide health problem. It is imperative, therefore, to find new and more effective means of treating this devastating disease. Considerable efforts should also be allocated to prevention as well as improvement of early detection before the later stages of the disease develop and the condition becomes irreversible. Unfortunately, the research funding for these efforts continues to be inadequate.

Our collaborative work on CNS effects of peptides (MSH, MIF1, TRH, LHRH, Somatostatin) has demonstrated that hypothalamic neuro-hormone analogs can affect CNS functions. These studies suggest that neuroendocrine mechanisms could play an important role in the development of neurological conditions, and turned out to be not only important and influential but also exceedingly useful for our decision to investigate the effects of antagonistic analogs of growth hormone-releasing hormone(GH-RH) in experimental models of Alzheimer’s disease. Our early generated GHRH antagonist of MZ class was shown to correct the impairment of memory consolidation, to have mild anxiolytic and antidepressive-like action when used in mice and rat models of the ?-amyloid toxicity, and also improved telomerase activity, oxidative stress, cognition, and increased the life expectancy in mice models of aging.

Profound changes on pituitary-gonadal axis are associated with neuronal damage and activation of brain immune cells, stimulating them to produce inflammatory cytokines. In turn, the resultant excess of cytokines contributes to an increase in the production of toxic ?-amyloid 1-42 (A?1-42) plaques. This suggests that neuro-inflammation may be a potential therapeutic target. This theory prompted our decision of testing GHRH antagonists in the CNS models due to their suppression of inflammatory pathways and anti-oxidative effects. We generated more potent GHRH antagonists to continue our studies on CNS and different models of AD. The new MIA class delayed the deterioration of cognitive performance in the Morris Water Maze task. Particularly MIA-690 inhibited the concentration of A?1-42 and Tau filaments, and the tissue expression of AD related genes in the brains of treated 5XFAD mice a well-established model of Alzheimer’s disease. We also observed attenuation of oxidative stress in human cortical cell cultures.

Thus our investigations suggest that GHRH antagonists can affect the cascade of Alzheimer’s disease by decreasing the aggregation and proteo-toxicity of A? and attenuating the accumulation of tangles of Tau protein. However, the mechanism of action of GHRH antagonists in models of AD must be clarified. GHRH and GHRH agonists have also been shown to exert effects on CNS and to

improve cognitive function in human subjects with mild cognitive impairment. The use of GHRH analogs could be also considered for other neurologic conditions such as posttraumatic stress disorder (PTSD), traumatic brain injury (TBI) and Gulf War Illness (GWI) which profoundly affect many US veterans of the wars such as those in Iraq and Afghanistan. Many patients with these disorders show low levels of GH associated with cognitive disorders, including US veterans diagnosed with blast concussion.

All these findings have profound implications on possible clinical applications of GHRH analogs, the list of which is continuously growing. Collectively these developments suggest that analogs of GHRH may find a variety of uses in the therapeutic armamentarium of neurodegenerative diseases and conditions.

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Publication

Endocrine approaches to treatment of Alzheimer's disease and other neurological conditions: Part I: Some recollections of my association with Dr. Abba Kastin: A tale of successful collaboration.
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Endocrine approaches to treatment of Alzheimer's disease and other neurological conditions: Part II: Some features of Alzheimer's disease.
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Endocrine approaches to treatment of Alzheimer's disease and other neurological conditions: Part III: Experimental studies on antagonist of LH-RH and GH-RH in animal models of Alzheimer's disease: Projections for treatments of other neurological conditions.
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