Designing Therapeutics for Neurodegenerative Diseases, with an Emphasis on Alzheimer's Disease

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With the graying of the Japanese and U.S. populations, once a rarity, neurodegenerative diseases have now become common, and Alzheimer's disease (AD) is the most prevalent of these. AD robs the elderly of their senses and is characterized by a progressive dementia that results from the dysfunction and death of neurons in the hippocampus and associated regions of the limbic system and cerebral cortex. These abnormalities result, in large part, from the over production and accumulation of amyloid-β peptide (Aβ) within and around neurons. This generates oxidative stress, perturbed calcium homeostasis, synapse loss and, eventually, cell death. Aβ is a core constituent of amyloid plaques and results from catalytic cleavage of a larger integral membrane protein, amyloid-β precursor protein (APP), by β- and γ-secretase activities. A loss of presynaptic markers of the cholinergic system and a subsequent down-regulation of post-synaptic elements in the described brain areas principally underpins AD memory processing and learning detriments. Acetylcholinesterase (AChE) inhibition is a useful treatment strategy for AD to augment deficient cholinergic function, and methods to reduce brain Aβ levels may slow disease progression. In addition, an overproduction of APP is associated with Down's syndrome (DS) and analysis of variants links a loss of cholinergic neurons in DS to an increase in APP levels prior even to Aβ accumulation, signifying that agents which safely lower APP and its cleaved toxic derivatives may offset AD and the dementia associated with DS.

Our development of physostigmine-based carbamates has resulted in novel, reversible and centrally active anticholinesterases, exemplifed by the AChE inhibitor and AD experimental drug, phenserine (*Curr Alz Res* 2:281-90, 2005). This agent also lowers APP and Aβ in cell culture, rodents and humans via non-cholinergic actions (*PNAS* 98:7605-10, 2001). AChE inhibition is invariably dose-limiting in rodents as well as in humans. Our further studies have resulted in novel, reversible and selective butyrylcholinesterase (BChE) inhibitors, typified by the clinical candidate bisnorcymserine, that provide the classic cholinergic actions of AChE inhibition without their traditional dose-limiting side effects, and retain actions to lower APP and Aβ (*PNAS* 102:17213-8, 2005). Our recent studies have additionally provided cholinergically inert compounds, exemplified by our AD experimental drug Posiphen, with primary actions on APP and Aβ (*J Pharmacol Exp Ther* 318:855-62, 2006). Posiphen and analogues dose-dependently lower $A\beta_{40}$ and $A\beta_{42}$ levels in human neuroblastoma cells in culture and in rodent brain after systemic administration via post-transcriptional mechanisms at the level of translational regulation of APP synthesis. These compounds are in current assessment as AD drug candidates and additionally are being used as pharmacological tools to elucidate mechanisms underpinning AD.

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