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FILE: ▪ Huperzine A
▪Alzheimer's Disease
▪ Neuroprotective Effects

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RE: Neuroprotective Effects of Huperzine A

Zhang HY and Tang XC. Neuroprotective effects of huperzine A: new therapeutic targets for neurodegeneration disease. *TIPS*. 2006;27(12):619-625.

In recent years, the most common pharmacological treatment for Alzheimer's disease has been acetylcholinesterase (AChE) inhibitors, most of which are suitable only for mild to moderate disease. However, this single-target approach has limited efficacy, and there is evidence that a multitarget approach might be more effective.

Huperzine A (HupA), a novel *Lycopodium* alkaloid isolated from the herb toothed clubmoss (*Huperzia serrata*), is a potent, reversible, selective and well-tolerated inhibitor of AChE. However, recent data indicate that the specific AChE inhibitory effect of HupA is only one aspect of its clinical and experimental efficacy compared with pure AChE inhibitors, which have only limited success in Alzheimer's disease therapy. This review focuses on the novel effects and mechanisms of HupA on β-amyloid precursor protein (APP) processing, β-amyloid-associated neurotoxicity, nerve growth factor (NGF), and neurotransmitter systems, thus highlighting its potential as a therapeutic agent that may target different pathologies.

Excessive accumulation of β-amyloid in the brain is one of the major characteristics of Alzheimer's disease and a possible cause of neurodegeneration. β-Amyloid originates from APP and is one of the main components of senile plaques. Abnormal processing of APP through the amyloidogenic pathway causes the buildup of these β-amyloid plaques. Studies show that HupA improves APP processing and reduces accumulation of β-amyloid in the brain.

Previous studies suggest that secretory-APP, which is produced by the nonamyloidogenic pathway, has potent neurotrophic and neuroprotective activities. HupA can affect the nonamyloidogenic pathway by increasing secretory-APP.

HupA was shown to possess protective effects against various apoptosis (programmed cell death) models. Studies reveal that HupA has an antioxidant effect not only in β-amyloid-induced models, but also in other cases. This effect is mediated by increasing levels of antioxidant enzymes and decreasing products of lipid peroxidation.

Decreased supply of NGF to basal forebrain acetylcholine-containing neurons leads to loss of neuronal markers and shrinkage, phenotypically mimicking what is observed in Alzheimer's disease. HupA ameliorates the cognitive deficiency of transient cerebral ischemia. Also, it enhances mRNA and protein levels of NGF, and other neuronal-enhancing proteins. However, the mechanisms by which HupA increases NGF secretion are not completely understood.

After HupA administration, noradrenaline, dopamine, and acetylcholine levels are markedly increased. These results suggest that the neuroprotective effects of HupA on β-amyloid toxicity might be helpful in recovering the acetylcholine, dopamine, and noradrenaline levels in Alzheimer's disease or other neurodegenerative diseases with abnormalities in these neurotransmitters.

HupA also acts on glutamate-mediated excitatory neurotransmission systems. Pretreatment with HupA significantly reduces both glutamate and NMDA-induced toxicity in cultured primary neuronal cells and reduces glutamate-induced calcium mobilization. These results indicate that HupA may act as an NMDA antagonist. Because the combination of an NMDA antagonist (memantine) and an AChE inhibitor (donepezil) has been reported to be successful in Alzheimer's disease therapy, HupA might serve as part of an alternative strategy.

HupA can target several molecular sites. The multiple effects of HupA on NGF, APP processing, and β-amyloid neurotoxicity might stimulate endogenous protective processes or promote repair of damaged structures and may be suited for treatment of conditions such as Parkinson's disease, amyotrophic lateral sclerosis, or Huntington's disease. HupA is currently in a trial for the therapy of Alzheimer's disease in China. It is also undergoing clinical trials in the US for the treatment of age-related memory deficiency. Although the possibilities of HupA look promising, further clinical study is needed.

—Jennifer Minigh, PhD

The American Botanical Council has chosen not to reprint the original article.