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Old Chinese Herbal Medicine Used for Fever Yields Possible New Alzheimer Disease Therapy

A COMPOUND first isolated from a traditional Chinese herbal medicine may lead to new therapeutic agents for Alzheimer disease (AD). Based on laboratory and x-ray crystallography studies, these agents, some researchers think, could be even better than the 2 drugs already approved for the disease.

The alkaloid compound, huperzine A (HupA), was discovered in the Chinese herbal medicine *Qian Ceng Ta*. This traditional remedy, which is prepared from the moss *Huperzia serrata*, has been used in China for centuries to treat fever and inflammation.

Although it has no antipyretic or anti-inflammatory properties, HupA does appear to be a potent inhibitor of acetylcholinesterase (AChE). In addition to appearing more selective and possibly less toxic than the 2 AChE inhibitors currently approved for the treatment of AD, HupA has a number of other pharmacological properties of clinical interest, said Israel Silman, PhD, professor of neurobiology at the Weizmann Institute of Science, Rehovot, Israel, who with colleagues worked out the 3-dimensional structure of the complex that forms when HupA binds to AChE (*Nat Struct Biol*. 1997;4:57-63). The data from this study will help the researchers design potentially more potent and selective analogues, said coauthor Joel Sussman, PhD, professor of structural biology at the Weizmann Institute and head of the Protein Data Bank at the Brookhaven National Laboratory in Upton, NY.

Although the purified compound has been used as a prescription drug for treating dementia in China for the past few years, clinical trials in the United States are only in the planning stage. Reports from China, where an estimated 100 000 people have been treated, suggest that the drug has low toxicity, said another coauthor, Alan Kozikowski, PhD, professor of pharmacy at Georgetown University's Institute of Cognitive and Computational Sciences, Washington, DC. Kozikowski is the researcher who first synthesized HupA in 1991.

Like tacrine hydrochloride, which the FDA approved for AD in 1993, and donepezil (Aricept; marketed by Eisai America, Inc, Teaneck, NJ, and Roerig Division of Pfizer, Inc, New York, NY), which was just approved (*JAMA*. 1997; 277:10), HupA is a reversible AChE inhibitor that prevents the degradation of endogenous acetylcholine. AChE nor-

mally plays a vital housekeeping role by breaking down excess acetylcholine. However, biopsy and postmortem studies have shown that there is a substantial loss of presynaptic cholinergic neurons in brains of patients with AD (*JAMA*. 1994;271:985-991). Whatever acetylcholine is produced in the brains of patients is quickly broken down by AChE and the shortage of the neurotransmitter appears to contribute to patients' memory loss and other cognitive defects.

'Ingeniously Designed Fit'

Acetylcholinesterase inhibitors like tacrine and donepezil work by jamming the cutting machinery of the AChE molecule. Previously, Sussman and coauthors Michal Harel, PhD, Silman, Felix Frolow, PhD, and Lilly Toker worked out the 3-dimensional structure of AChE and showed that the molecule has a deep chasm known as the active-site gorge, which the researchers think guides acetylcholine molecules into the enzyme's cutting machinery (*Science*. 1991;253:872-879). The investigators then worked out the 3-dimensional structure of the complex formed when a molecule of tacrine jams the active-site gorge (*Proc Nat Acad Sci USA*. 1993; 90:9031-9035).

"HupA appears to bind more tightly and specifically to acetylcholinesterase than the other AChE inhibitors," Sussman said. "It is as if this natural substance were ingeniously designed to fit into the exact spot in acetylcholinesterase where it will do the most good." Compared with tacrine and donepezil, HupA has a longer half-life and the AChE-HupA complex has a slower rate of dissociation, which may make it a more effective therapeutic agent, Kozikowski added.

The 3-dimensional structure of the AChE-HupA complex was worked out by Weizmann Institute of Science graduate student Mia Raves, along with Sussman, Harel, and Silman. It also involved close collaboration with Kozikowski and Yuan-Ping Pang, PhD, associate consultant in synthetic and computational chemistry at the Mayo Clinic, Jacksonville, Fla, whose theoretical predictions helped in the analysis of the structure of the complex, Sussman said.

A substantial percentage of patients taking tacrine or donepezil experience adverse cholinergic effects that cause some to discontinue therapy. In addition

to the cholinergic effects such as nausea, vomiting, salivation, sweating, and lacrimation, tacrine is hepatotoxic (*JAMA*. 1994;271:992-993). According to Kozikowski, HupA appears to be strongly specific for AChE, and such specificity suggests that it may be effective with fewer adverse effects.

May Also Protect Neurons

Huperzine A appears to have additional pharmacological properties that make it an attractive candidate therapy for clinical trials. In studies using cultures of cells from the hippocampus and cerebellum of rat embryos, other researchers have shown that HupA decreases neuronal cell death caused by toxic levels of glutamate (*NeuroReport*. In press). In addition to the loss of cholinergic function in patients with AD, glutamatergic and GABAergic neurotransmitter systems may also be compromised, said author Bhupendra P. Doctor, PhD, director of the Walter Reed Army Institute of Research's Division of Biochemistry, Washington, DC. Glutamate activates N-methyl-D-aspartate receptors and increases the flux of calcium ions into the neurons, which in sufficient concentration can kill the cells. This property may make HupA a potential drug for reducing neuronal injury from strokes, epilepsy, and other disorders, he said.

Doctor, Yacov Ashani, PhD, and colleagues at the Israel Institute for Biological Research, Ness-Ziona, Israel, have also been testing HupA as a prophylactic drug against soman and other nerve gas poisons (*Life Sci*. 1994;54:991-997). Its long-lasting antidotal efficacy and low toxicity make this drug promising as a protective agent against chemical weapons, he said.

The 3-dimensional structure of HupA, which can be seen on Brookhaven's Protein Data Bank's web page (<http://www.pdb.bnl.gov>), is already helping researchers rationally design synthetic analogues with improved therapeutic properties. For example, based on their modeling studies, Sussman and colleagues predicted that adding a methyl group at a certain spot on the molecule would improve its ability to inhibit AChE. When other researchers tested the new agent, it displayed 8 times greater affinity for the enzyme than does the natural compound, he said.

—by Andrew A. Skolnick