REVIEW ARTICLE

HUPERZINE A - AN INTERESTING ANTICHOLINESTERASE COMPOUND FROM THE CHINESE HERBAL MEDICINE

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Summary: Huperzine A, alkaloid from the Chinese herbal medicine Qian Ceng Ta, which is prepared from the moss *Huperzia serrata*, has been used in China for centuries to treat fever and inflammation. Huperzine A is a strong inhibitor of cholinesterases with high selectivity to acetylcholinesterase and in China is developed as therapeutic against Alzheimer's disease. May be that huperzine A will be better than other centrally active anticholinesterases in treating this neurodegenerative disorder. Huperzine A appears to have additional pharmacological properties that make it an attractive candidate therapy for clinical trials.

Key words: *Huperzine A; Alkaloid; Inhibitor of Acetylcholinesterase; Alzheimer's Disease; Treatment*

Introduction

The alkaloid compound, huperzine A, was discovered in the Chinese herbal medicine called Qian Ceng Ta (14). This traditional remedy, which is prepared from the moss *Huperzia serrata*, has been used in China for centuries to treat fever and inflammation.

Chemistry

Huperzine A is an unsaturated sesquiterpenic compound with pyridone moiety and primary amino group (Fig. 1) $C_{15}H_{18}N_2O$, MW = 242.32. Chemically 9-amino-13-ethylidene-11-methyl-4-azatricyclo[7.3.1.0(3.8)]tridec a-3(8),6,11-trien-5-one. Compound is optically active and in the moss is present only its (-)-enantiomer. The pyridone ring is planar and the stereochemistry of the C(11)-C(12) double bond is E. It is white solid soluble in aqueous acids and $CHCl_3$ (3).

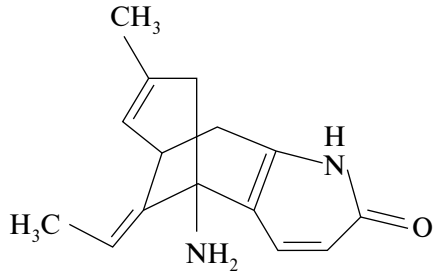

Fig. 1: Chemical structure of huperzine A

Biochemistry

Huperzine A is a potent reversible inhibitor of cholinesterases, i.e. acetylcholinesterase (AChE) and butyrylcholinesterse (BuChE) with on- and off-rates that depend on both the type and the source of enzyme. A low dissociation constants Ki was obtained for mammalian-AChE-huperzine A (20-40 nM) compared to mammalian BuChE-huperzine A (20-40 μM) (1). This indicates that the thermodynamic stability of huperzine-cholinesterase complex may depend on the number and type of aromatic amino acid residues in the catalytic pocket region of the enzyme molecule. The mechanism of the inhibition of acetylcholinesterase (AChE) is stereoselective. (-)-Huperzine A, which is in drug, was the more potent enantiomer with a Ki value of 8 nM. (+)-Huperzine A inhibited the enzyme 38-fold less potently with a Ki value of 300 nM. Racemic huperzine A was about two-fold less potent than the more active enantiomer. The mechanism of inhibition of rat cortical AChE for all three compounds was of the mixed linear competitive type (9). Very similar results were obtained with enzymes from other sources (13). The crystal structure of the complex of AChE with optically pure huperzine A at 2.5 A resolution shows an unexpected orientation for the inhibitor with surprisingly few strong direct interactions with protein residues to explain its high affinity. An analysis of the affinities of structural analogues of huperzine A, correlated with their interactions with the protein, shows the importance of individual hydrophobic interactions between huperzine A and aromatic residues in the active-site gorge of AChE (12, 13). Based on docking studies and the pharmacologi-

cal results reported for huperzine A and its analogues, it was predicted that huperzine A binds to the bottom of the binding cavity of AChE with its ammonium group interacting with Trp84, Phe330 and Asp72 and to the opening of the gorge with its ammonium group partially interacting with Trp279. At the catalytic site, three partially overlapping subsites of huperzine A were identified which might provide a dynamic view of binding of huperzine A to the catalytic site (7, 10).

Neurochemistry

AChE was assessed in rats after acute and chronic administration of huperzine A. Forty-five min after a single injection of huperzine A (0.5 mg/kg, i.p.) the activity of AChE was significantly decreased by 15 - 30 per cent in hippocampus, striatum and septum. The activity of cholineacetyl transferase (ChAT) was not altered. In the hippocampus high affinity choline transport (HACT) was altered by 25 per cent, whereas no effect in the striatum was observed. After 90 min, both inhibition of AChE and attenuation of HACT had returned to control values. After 7 days chronic application of huperzine A (twice a day) at 0.5 mg/kg, the activity of AChE was significantly reduced by 20 -30 per cent in every region of the brain studied. HACT in the hippocampus was reduced by 28 per cent, 45 min after the last injection, but in the striatum there was no effect. The activity of ChAT was not affected in any region of the brain studied (8).

Tang et al. (15) show that huperzine A can produce a long-term inhibition of AChE activity in the acetylcholine levels up to 40 per cent at 60 min. There is considerable regional variation in the degree of acetylcholine elevation after huperzine A with maximal values seen in frontal (125 per cent) and parietal (105 per cent) cortex and smaller increases (22-65 per cent) in other brain regions. A comparable effect was also observed in studies, in which, over a range of 0.1-2.0 mg/kg of huperzine A administered i.p., significantly inhibits of AChE activity in all brain region tested (hippocampus, hypothalamus, striatum and frontal cortex) and decreases level of brain acetylcholine (16).

Pharmacology

Huperzine A at concentrations 1 to 100 μM does not significantly alter the electrically evoked release of ^{3}H-acetylcholine from cortical slices. With the exception of the highest concentrations (600 M) the displacement effect of huperzine A for cholinergic ligands is -stronger for ^{3}H-nicotine than for ^{3}H-QNB. Autoradiographic study in the mouse shows that 60 min after i.v. injection (183 μg/kg) huperzine A is particularly concentrated in certain areas such as frontoparietal cortex, nucleus accumbens, hippocampal, and striatal cortex. Radioactivity is practically absent in the whole body at 12 hr (15).

Huperzine A in doses from 0.4 o 0.5 mg/kg, i.p., significantly ameliorated the AF64A-induced memory deficit in rats in the radial maze. These results suggest that dissrupting working memory induced by cholinotoxine AF64A can be effectively ameliorated by huperzine A (18). Very similar effects were obtained with huperzine A in doses from 0.1 to 0.4 mg/kg, p.o., on memory impairments induced by scopolamine. The comparison with other AChE inhibitors shows that huperzine A is the most selective AChE inhibitor, and improved the working memory deficit significantly better than did tacrine or donepezil (2).The results with natural (-)-huperzine A and synthetic (+/-)-huperzine A indicate a similar biological effects, but the racemic mixture of (+/-)-huperzine A has a weaker biological activity than the natural product (6).

Huperzine A in dose 0.1 mg/kg, in conscious rabbits produced, already 30 sec after i.v. administration, an alert EEG pattern, which showed decreases of lower frequency components and the total EEG power in cortical area, and the dominant frequency transferred from delta rhythm to theta rhythm in hippocampus and the same effects were obsereved with physostigmine in the dose of 0.1 mg/kg. Intravenously administered huperzine A in dose 0.2 mg/kg as well as physostigmine in dose 0.3 mg/kg antagonized the EEG effects of scopolamine (0.3 mg/kg i.v.). That results indicate that the effects of huperzine A are closely related to the action on the central cholinergic system (5).

Huperzine A appears to have additional pharmacological properties that make it an attractive candidate therapy for clinical trials. In studies using cell cultures from the hippocampus and cerebellum of rat embryos, have been shown that huperzine A decreases neuronal cell death caused by toxic level of glutamate (14). In addition to the loss of cholinergic function in patients with AD, glutamatergic and GABAergic neurotransmitter systems may also be compromised. 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.

Huperzine A has been also testing as a prophylactic drug against soman and other nerve gas poisoning with very good effect (4).

Pharmacokinetics

Pharmacokinetic of huperzine A was studied in six volunteers after a single oral dose of 0.99 mg and drug concentrations were assayed by reverse phase HPLC from 0.5 to 10 hrs. The time course of plasma concentrations conformed to a one-compartment open model with a first order absorption with $T_{0.5\ ka}$ = 12.6 min, $T_{0.5\ ke}$ = 288.5 min, T_{max} = 79.6 min, C_{max} = 8.4 μg/litre, AUC = 4.1 mg/litre.min. From this result is clear that huperzine A is absorbed rapidly, distributed widely in the body, and eliminated at a moderate rate (11).

Medical use

Huperzine A has similar action to the drugs currently approved to treat Alzheimer's disease - tacrine (Cognex) and donepezil (Aricept), i.e. inhibits brain AChE and blocks the breakdown of acetylcholine, a chemical messenger in the brain that is important to memory function (14, 19). Reports from China, where perhaps 100,000 people have used huperzine A, suggest that it is at least as safe as the two approved Alzheimer's drugs. Not all informations from China are available and trustworthy. It is evident that huperzine A in China was not only clinically tested, but this compound is used as remedy in the form of tablets in Alzheimer's disease (17). Nevertheless, huperzine A is probably still a long way to medical use in Europe (14).

The ability of huperzine A to decrease neuronal cell death caused by toxic level of glutamate may make this compound a potential drug for reducing neuronal injury from strokes, epilepsy, and other disorders.

Huperzine A is a candidate drug against organophosphate nerve agent toxicity for its long-lasting antidotal efficacy and low toxicity (4). Prophylactic study make this drug promissing as a protective agent against chemical weapons.

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