Neuro Endocrinol Lett. 2011;32 Suppl 1:95-100.

# Huperzine induces alteration in oxidative balance and antioxidants in a guinea pig model.

Pohanka M, Hrabinova M, Zemek F, Drtinova L, Bandouchova H, Pikula J.

## Source

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## Abstract

**OBJECTIVES:**

Alzheimer's disease (AD) is a neurodegenerative disorder. Symptomatic treatment is available by inhibitors of acetylcholinesterase (AChE) such as rivastigmine, galantamine and donepezil. As huperzine is a promising compound for AD treatment, our study was aimed at evaluating its pertinent implications in oxidative stress.

**METHODS:**

Laboratory guinea pigs were exposed to huperzine A at doses of 0, 5, 25, 125 and 625 μg/kg. The animals were observed for cognitive disorders and sacrificed one hour after exposure. Tonic-clonic seizures were noticed, but only in highly dosed animals. Ferric reducing antioxidant power (FRAP), thiobarbituric acid reactive substances (TBARS), glutathione reductase and glutathione S-transferase were assessed in frontal, temporal and parietal lobes, the cerebellum, liver, spleen and kidney.

**RESULTS:**

Only minimal changes in enzymatic markers were recognized. Huperzine was not implicated in oxidative stress enhancement as the TBARS values remained quite stable. Surprisingly, antioxidants accumulated in the examined brain compartments as the FRAP value was significantly elevated following all doses of huperzine.

**CONCLUSIONS:**

We discuss the potency of huperzine in enhancing the antioxidant capacity of the central nervous system. Huperzine is probably implicated in more processes than cholinesterase inhibition only.

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22167216
[PubMed - indexed for MEDLINE]

J Alzheimers Dis. 2012 Jan 1;31(1):131-42.

# Decreased Accumulation of Subcellular Amyloid-β with Improved Mitochondrial Function Mediates the Neuroprotective Effect of Huperzine A.

Yang L, Ye CY, Huang XT, Tang XC, Zhang HY.

## Source

State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, China.

## Abstract

A number of recent discoveries indicate that huperzine A, an active herbal medicine employed for the treatment of Alzheimer's disease (AD) in China, can afford neuroprotection on in vitro and in vivo models related to mitochondrial dysfunction. However, it is an intricate and highly debated research topic about whether another pharmacological mechanism is involved in the beneficial profiles of huperzine A, independent of its well-recognized potent acetycholinesterase (AChE) inhibitory effect. As an extension, this study for the first time verified the co-occurrence of the beneficial effects of huperzine A on mitochondrial dysfunction and memory deficits in AβPP/PS1 double transgenic mice, at a time point that AChE was not inhibited. Moreover, using isolated brain cortical mitochondria, we confirmed the ameliorating effect of huperzine A on oligomeric Aβ1-42-induced ATP reduction and mitochondrial swelling, as well as a decrease in the enzymatic activities of respiratory chain complexes, especially complex II-III and complex IV, which may be attributed to the blockage of oligomeric Aβ1-42 from penetrating into mitochondria. These results shed more light on a potential direct target of huperzine A on isolated mitochondria, which may be largely different from its specific inhibition on AChE. This work describes a novel mechanism of neuroprotection by huperzine A and provides important clues for discovering novel therapeutic strategy for AD.

PMID:
22531425
[PubMed - in process]

Chem Biodivers. 2011 Jul;8(7):1189-204. doi: 10.1002/cbdv.201000269.

# Huperzine a as potential treatment of Alzheimer's disease: an assessment on chemistry, pharmacology, and clinical studies.

Ha GT, Wong RK, Zhang Y.

## Source

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## Abstract

Alzheimer's disease (AD) is the fourth leading cause of death in adults, characterized by hallmark neuritic plaques and neurofibrillary tangles. Current treatments focus only on symptom relief. As a possible new treatment option for AD, huperzine A's chemistry, pharmacology, and clinical effectiveness are assessed. The chemical synthesis of huperzine A has been optimized, while an in vitro technique has provided a renewable plant source. Pharmacological studies showed that the drug inhibits the enzyme acetylcholinesterase reversibly and selectively. Huperzine A also displayed good pharmacokinetics with a rapid absorption and a wide distribution in the body at a low to moderate rate of elimination. Presently, inadequate toxicity data in human have been reported, yet animal studies demonstrated mild to moderate cholinergic side effects at therapeutic doses. Previous clinical trials have shown improvement in memory function using MMSE, MQ, ADAS-COG, and ADL tests. In an unpublished phase II clinical trial, the ADAS-COG and MMSE tests indicated cognitive enhancement at a dose of 0.4 mg, yet no improvement was observed at a dose of 0.2 mg. The MMSE scores indicated cognitive enhancement at 0.4 mg. Promising data suggested that huperzine A is well tolerated at doses up to 0.4 mg for 24 weeks. Therefore, huperzine A seems to be a potential treatment option for AD.



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21766442
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Mini Rev Med Chem. 2011 Sep;11(10):836-42.

# An overview on natural cholinesterase inhibitors--a multi-targeted drug class--and their mass production.

Orhan IE, Orhan G, Gurkas E.

## Source

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## Abstract

Cholinesterase enzyme family consisting of acetylcholinesterase (AChE) and butrylcholinesterase (BChE) is important in pathogenesis of Alzheimer's disease (AD), explained by "cholinergic hypothesis". Accordingly, deficiency of the neuromediator called "acetylcholine" excessive amount of BChE has been well-described in the brains of AD patients. Consequently, cholinesterase inhibition has become one of the most-prescribed treatment strategies for AD. In fact, cholinesterase inhibitors have been also reported for their effectiveness in some other diseases including glaucoma, myasthenia gravies, as well as Down syndrome, lately. They play a role in the action of mechanism of insecticidal drugs such as carbamate derivatives as well as nerve gases such as malathion and parathion. All these utilizations can make them a multi-targeted drug class putting a special emphasis on AD therapy in the first place. Several inhibitors of cholinesterases with synthetic and natural origins are available in drug market; however, the reasons including side effects, relatively low bioavailability, etc. limit their uses in medicine and there is still a great demand to discover new cholinesterase inhibitors. Galanthamine, an alkaloid derivative isolated from snowdrop (Galanthus nivalis L.), is the latest anticholinesterase drug used against AD. Huperzine A, isolated from Huperzia serrata (Thunb.) Trev. is the most-promising drug candidate with potent anticholinesterase effect and it is a licensed anti-AD drug in China. In this review, a short introduction will be given on known cholinesterase inhibitors and, then, galanthamine and huperzine A will be covered in regard with their cholinesterase inhibitory potentials and mass productions by organic synthesis and in vitro culture techniques.

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21762104
[PubMed - indexed for MEDLINE]

Neurology. 2011 Apr 19;76(16):1389-94.

# A phase II trial of huperzine A in mild to moderate Alzheimer disease.

Rafii MS, Walsh S, Little JT, Behan K, Reynolds B, Ward C, Jin S, Thomas R, Aisen PS; Alzheimer's Disease Cooperative Study.

## Collaborators (21)

## Source

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## Abstract

**OBJECTIVE:**

Huperzine A is a natural cholinesterase inhibitor derived from the Chinese herb Huperzia serrata that may compare favorably in symptomatic efficacy to cholinesterase inhibitors currently in use for Alzheimer disease (AD).

**METHODS:**

We assessed the safety, tolerability, and efficacy of huperzine A in mild to moderate AD in a multicenter trial in which 210 individuals were randomized to receive placebo (n = 70) or huperzine A (200 μg BID [n = 70] or 400 μg BID [n = 70]), for at least 16 weeks, with 177 subjects completing the treatment phase. The primary analysis assessed the cognitive effects of huperzine A 200 μg BID (change in Alzheimer's Disease Assessment Scale-cognitive subscale [ADAS-Cog] at week 16 at 200 μg BID compared to placebo). Secondary analyses assessed the effect of huperzine A 400 μg BID, as well as effect on other outcomes including Mini-Mental State Examination, Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change scale, Alzheimer's Disease Cooperative Study Activities of Daily Living scale, and Neuropsychiatric Inventory (NPI).

**RESULTS:**

Huperzine A 200 μg BID did not influence change in ADAS-Cog at 16 weeks. In secondary analyses, huperzine A 400 μg BID showed a 2.27-point improvement in ADAS-Cog at 11 weeks vs 0.29-point decline in the placebo group (p = 0.001), and a 1.92-point improvement vs 0.34-point improvement in the placebo arm (p = 0.07) at week 16. Changes in clinical global impression of change, NPI, and activities of daily living were not significant at either dose.

**CONCLUSION:**

The primary efficacy analysis did not show cognitive benefit with huperzine A 200 μg BID. Classification of evidence: This study provides Class III evidence that huperzine A 200 μg BID has no demonstrable cognitive effect in patients with mild to moderate AD.

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21502597
[PubMed - indexed for MEDLINE] PMCID: PMC3269774

Neuropsychopharmacology. 2011 Apr;36(5):1073-89. Epub 2011 Feb 2.

# Huperzine A activates Wnt/β-catenin signaling and enhances the nonamyloidogenic pathway in an Alzheimer transgenic mouse model.

Wang CY, Zheng W, Wang T, Xie JW, Wang SL, Zhao BL, Teng WP, Wang ZY.

## Source

China Medical University, Shenyang, China.

## Abstract

Huperzine A (HupA) is a reversible and selective inhibitor of acetylcholinesterase (AChE), and it has multiple targets when used for Alzheimer's disease (AD) therapy. In this study, we searched for new mechanisms by which HupA could activate Wnt signaling and reduce amyloidosis in AD brain. A nasal gel containing HupA was prepared. No obvious toxicity of intranasal administration of HupA was found in mice. HupA was administered intranasally to β-amyloid (Aβ) precursor protein and presenilin-1 double-transgenic mice for 4 months. We observed an increase in ADAM10 and a decrease in BACE1 and APP695 protein levels and, subsequently, a reduction in Aβ levels and Aβ burden were present in HupA-treated mouse brain, suggesting that HupA enhances the nonamyloidogenic APP cleavage pathway. Importantly, our results further showed that HupA inhibited GSK3α/β activity, and enhanced the β-catenin level in the transgenic mouse brain and in SH-SY5Y cells overexpressing Swedish mutation APP, suggesting that the neuroprotective effect of HupA is not related simply to its AChE inhibition and antioxidation, but also involves other mechanisms, including targeting of the Wnt/β-catenin signaling pathway in AD brain.

PMID:
21289607
[PubMed - indexed for MEDLINE]
PMCID:
PMC3077275

Nutr Neurosci. 2009 Aug;12(4):142-8.

# Green tea polyphenol (-)-epigallocatechin-3-gallate enhances the inhibitory effect of huperzine A on acetylcholinesterase by increasing the affinity with serum albumin.

Zhang L, Cao H, Wen J, Xu M.

## Source

Research Institute for Molecular Pharmacology and Therapeutics, Central South University, Changsha, Hunan, People's Republic of China.

## Abstract

The green tea polyphenol (-)-epigallocatechin-3-gallate (EGCG) was investigated for its enhancement effect of huperzine A on inhibiting acetylcholinesterase (AChE). The inhibitory effect of huperzine A on acetylcholinesterase is quite weak in the whole phase. EGCG hardly inhibits the AChE activity within the range 10-300 mg/kg. However, upon addition of EGCG to the huperzine A groups, a remarkably enhanced inhibitory effect was observed. The EGCG also can largely prolong the inhibitory time. These results indicate that addition of EGCG to huperzine A can reduce the dose of huperzine A required compared with huperzine A alone. The enhancement and complementary effect of EGCG on huperzine A activity may partly be due to the antioxidant property of EGCG. One of the beneficial effects of green tea is to induce a feeling of relief. It is conceivable that this function may be regulated by EGCG in the central nervous system since EGCG is distributed in the brain after oral administration. EGCG can be used as an enhanced supplement for huperzine A to treat Alzheimer's disease.

PMID:
19622237
[PubMed - indexed for MEDLINE]

Free Radic Biol Med. 2009 Jun 1;46(11):1454-62. Epub 2009 Mar 9.

# Huperzine A protects isolated rat brain mitochondria against beta-amyloid peptide.

Gao X, Zheng CY, Yang L, Tang XC, Zhang HY.

## Source

State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zu Chong Zhi Road, Zhangjiang Hi-Tech Park, Shanghai 201203, People's Republic of China.

## Abstract

Our previous work in cells and animals showed that mitochondria are involved in the neuroprotective effect of huperzine A (HupA). In this study, the effects of HupA on isolated rat brain mitochondria were investigated. In addition to inhibiting the Abeta(25-35) (40 microM)-induced decrease in mitochondrial respiration, adenosine 5'-triphosphate (ATP) synthesis, enzyme activity, and transmembrane potential, HupA (0.01 or 0.1 microM) effectively prevented Abeta-induced mitochondrial swelling, reactive oxygen species increase, and cytochrome c release. More interestingly, administration of HupA to isolated mitochondria promoted the rate of ATP production and blocked mitochondrial swelling caused by normal osmosis. These results indicate that HupA protects mitochondria against Abeta at least in part by preserving membrane integrity and improving energy metabolism. These direct effects on mitochondria further extend the noncholinergic functions of HupA.

PMID:
19272446
[PubMed - indexed for MEDLINE]

J Neural Transm. 2009 Apr;116(4):457-65. Epub 2009 Feb 17.

# Efficacy and safety of natural acetylcholinesterase inhibitor huperzine A in the treatment of Alzheimer's disease: an updated meta-analysis.

Wang BS, Wang H, Wei ZH, Song YY, Zhang L, Chen HZ.

## Source

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## Abstract

The objective of this study was to provide an updated meta-analysis of the efficacy and safety of huperzine A (HupA) in Alzheimer's disease (AD). We searched for randomized trials comparing HupA with placebo in the treatment of AD. The primary outcome measures were mini-mental state examination (MMSE) and activities of daily living scale (ADL). Data were extracted from four randomized clinical trials and analyzed using standard meta-analysis and meta-regression methods. Oral administration of HupA for 8-24 weeks (300-500 microg daily) led to significant improvements in MMSE and ADL. The results of meta-regression showed that the estimated effect size of MMSE and ADL was increased over the treatment time. Most adverse events were cholinergic in nature and no serious adverse events occurred. Huperzine A is a well-tolerated drug that could significantly improve cognitive performance and ADL in patients with AD.

PMID:
19221692
[PubMed - indexed for MEDLINE]

J Appl Toxicol. 2001 Dec;21 Suppl 1:S47-51.

# The NMDA receptor ion channel: a site for binding of Huperzine A.

Gordon RK, Nigam SV, Weitz JA, Dave JR, Doctor BP, Ved HS.

## Source

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## Abstract

Huperzine A (HUP-A), first isolated from the Chinese club moss Huperzia serrata, is a potent, reversible and selective inhibitor of acetylcholinesterase (AChE) over butyrylcholinesterase (BChE) (Life Sci. 54: 991-997). Because HUP-A has been shown to penetrate the blood-brain barrier, is more stable than the carbamates used as pretreatments for organophosphate poisoning (OP) and the HUP-A:AChE complex has a longer half-life than other prophylactic sequestering agents, HUP-A has been proposed as a pretreatment drug for nerve agent toxicity by protecting AChE from irreversible OP-induced phosphonylation. More recently (NeuroReport 8: 963-968), pretreatment of embryonic neuronal cultures with HUP-A reduced glutamate-induced cell death and also decreased glutamate-induced calcium mobilization. These results suggest that HUP-A might interfere with and be beneficial for excitatory amino acid overstimulation, such as seen in ischemia, where persistent elevation of internal calcium levels by activation of the N-methyl-D-aspartate (NMDA) glutamate subtype receptor is found. We have now investigated the interaction of HUP-A with glutamate receptors. Freshly frozen cortex or synaptic plasma membranes were used, providing 60-90% specific radioligand binding. Huperzine A (< or =100 microM) had no effect on the binding of [3H]glutamate (low- and high-affinity glutamate sites), [3H]MDL 105,519 (NMDA glycine regulatory site), [3H]ifenprodil (NMDA polyamine site) or [3H]CGS 19755 (NMDA antagonist). In contrast with these results, HUP-A non-competitively (Hill slope < 1) inhibited [3H]MK-801 and [3H]TCP binding (co-located NMDA ion channel PCP site) with pseudo K(i) approximately 6 microM. Furthermore, when neuronal cultures were pretreated with HUP-A for 45 min prior to NMDA exposure, HUP-A dose-dependently inhibited the NMDA-induced toxicity. Although HUP-A has been implicated to interact with cholinergic receptors, it was without effect at 100 microM on muscarinic (measured by inhibition of [3H]QNB or [3H]NMS binding) or nicotinic [3H]epibatidine binding) receptors; also, HUP-A did not perturb adenosine receptor binding [3H]PIA or [3H]NECA). Therefore, HUP-A most likely attenuates excitatory amino acid toxicity by blocking the NMDA ion channel and subsequent Ca2+ mobilization at or near the PCP and MK-801 ligand sites. Thus, on the one hand, HUP-A could be used as a pretreatment against OPs and it might also be a valuable therapeutic intervention in a variety of acute and chronic disorders by protecting against overstimulation of the excitatory amino acid pathway. By blocking NMDA ion channels without psychotomimetic side-effects, HUP-A may protect against diverse neurodegenerative states observed during ischemia or Alzheimer's disease.



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11920920
[PubMed - indexed for MEDLINE]

Neuroscience. 2001;105(3):663-9.

# Huperzine A, a nootropic alkaloid, inhibits N-methyl-D-aspartate-induced current in rat dissociated hippocampal neurons.

Zhang JM, Hu GY.

## Source

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## Abstract

Huperzine A, a nootropic alkaloid isolated from a Chinese herb, has been proposed as one of the most promising agents to treat Alzheimer's disease. Recently, the agent was found to inhibit the N-methyl-D-aspartate (NMDA) receptors in rat cerebral cortex in addition to causing an inhibitory effect on acetylcholinesterase. In the present study, the mechanisms underlying NMDA receptor inhibition were investigated using whole-cell voltage-clamp recording in CA1 pyramidal neurons acutely dissociated from rat hippocampus. Huperzine A reversibly inhibited the NMDA-induced current (IC(50)=126 microM, Hill coefficient=0.92), whereas it had no effect on the current induced by alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate or kainate. The effect was non-competitive, and showed neither 'voltage-dependency', nor 'use-dependency'. The IC(50) values of huperzine A were neither altered by changing the concentrations of glycine (2-0.2 microM) and pH (7.4-6.7) in the external solution, nor by addition of Zn(2+) (5 microM) and dithiothreitol (5 mM) to the external solution. However, addition of spermine (200 microM) to the external solution caused a parallel shift to the right of the huperzine A concentration-response curve. From these we suggest that huperzine A acts as a non-competitive antagonist of the NMDA receptors, via a competitive interaction with one of the polyamine binding sites. The potential relevance of NMDA receptor antagonist activity of huperzine A to the treatment of Alzheimer's disease is discussed.

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11516831
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