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Review Article

Mechanisms of Huperzine a as an Active Component of Traditional Chinese Medicine for Preventing and Treating Alzheimer's Disease

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SUMMARY

Huperzine a (Hup a) discovered in Chinese plant Lycopodium serratum Thunb has been used for preventing and treating Alzheimer's disease (AD) in recent years. It is a natural, efficient and reversible inhibitor of acetylcholinesterase (AChE), which has a significant effect on AD. With multiple pharmacological effects, Hup a is able to restrain AChE and memory impairment. In addition to this, it has several neuroprotective effects including influencing cholinergic neurotransmitters in the brain, protecting cerebral nerve cells and oxidative injuries induced by amyloid beta. In addition, the neuroprotective effect of Hup a is attributed to resist N-methyl-d-aspartate receptors and regulating nerve growth factor. Moreover, Hup a has effects on reducing iron in the brain for treating AD.

1. Introduction

Alzheimer's disease (AD) as a most widely seen dementia and progressive neurodegenerative disorder impacts approximately 24 million populations across the world. AD greatly damages higher mental functions and presents an injury of psychological and behavioral symptoms of aging patients. In recent years, some patients have been observed having degradation of acetylcholine neurons in basal forebrains. Cortical cholinergic innervations are involved in degenerative diseases, such as AD. Donepezi has effect on stimulus-driven attentional capture and increases intensity of the visual response and input.[1,2] In AD, it was found that cortical cholinergic axons show more severe decline and the capacity was weaken for neuroplasticity.[3] Involvement of Ch4 is associated with AD, but the mechanism is not clear.[4]

Huperzine a (Hup a) can significantly weaken the memory impairment neuronal damage ischemia and might be beneficial to restore choline acetyltransferase activity.[5] Currently, a novel mechanism is found for treating AD with Hup a which can decrease iron contents in brains and therefore treat AD. Apart from inhibiting transferrin-receptor 1 expression, Hup a also increases the content of transferrin-bound iron in cultured neurons.[6] By using Hup a, the phosphorylation of p44/p42 mitogen-activated protein (MAP) kinase and the A disintegrin and metalloproteinase domain 10 (ADAM10) level can be remarkably enhanced while acetylcholinesterase activities in neuroblastoma cells are suppressed.[7] Hup a plays a role in protecting neurons as it can reduce the down-regulation of anti-apoptotic gene, bcl-2 and the up-regulation of pro-apoptotic gene, bax, and antagonize the reduction of immunoreactive caspase-3 proenzyme.[8] Apart from the above functions, Hup a is effective in protecting PC12 cells from the toxicity caused by OGD and therefore improves survival.[9] These new findings of pharmacological mechanisms and properties of Hup a have greatly improved our understanding on the treatment of AD.

2. Effects on AChE activity

Despite having no antipyretic properties, Hup a appears to have been potent inhibition effect on AChE in deed.[10] Cholinergic neurotransmitter acetylcholine, as an important material in brains, its hydrolysis can be catalyzed by AChE.[11] Hup a, galanthamine and donepezil are possible AChE inhibitors against AD and are well AD drugs.[12] Hup a not only reversibly and selectively inhibits AChE but also has no side effects on cognition and behaviors.[13] Hup a exhibits a high inhibition and produces a relatively steady inhibition of AChE. In comparison, the inhibition intensity of Hup for AChE in cortex is 180 and 24 times respectively of tacrine and donepezil.[14] Due to improving working memory deficit caused by scopolamine, Hup a has been acted as an agent for treating cognitive impairment. Moreover, it shows superior effects than E2020 or tacrine in clinical treatment for AD.[15] Comparing with E2020 and tacrine, Hup a has better efficacy in inhibiting AChE in the hippocampus and cortex.[16]

Hup a can significantly decrease the AChE activity, shows a long action duration through transiently declining the high affinity choline transport in hippocampus in striatum, septum and hippocampus.[17] In addition, donepezil is the most effective inhibitors of G1 AChE, with different inhibition constants of these AChE inhibitors, Hup a exhibits a higher efficacy on the inhibition of G4.[18] Moreover, as it barely has directed interactions and protein residues, Hup a has surprisingly high affinity in active-site gorges of AChE.[19]

Distribution and accumulation of Hup a is mainly found in some

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areas of brains including hippocampal, striatal cortex, frontoparietal cortex and nucleus accumbens in mice.[20] *In vitro* Hup a more apparently inhibit AChE activities than physostigmine.[21] Hup a significantly decreases the activity of AChE by 20–30% for chronic treatment. Moreover, it cuts down 28% of the high affinity choline transport of AChE in the hippocampus. In addition, in neuroblastoma cells, 20% of AChE activity are inhibited by Hup a.[22]

3. Mechanism of protecting the neurondamage and cell apoptosis

In rats with damaged nucleus basalis of meynert (NBM), Hup a is able to produce cortical desynchronization, reduce in theta power, restore electroencephalogram (EEG) architecture, improve theta oscillation, decrease the injure in attention/working memory and reduce spatial navigation performance in the behavioral tasks in the hippocampus.[23] In SH-SY5Y cells, Aβ significantly increases the mRNA expressions including NTN4, NFAT5, RAC2, EPHA1 and LIMK1. Hup a up-regulates NTN4, NFAT5, and LIMK1 markedly, but decreases the expressions of RAC2, SEMA4F, PAK2 and LICAM. It has been found that Hup a is able to improve and regulate the Aβ-induced damage of neurite outgrowth related genes.[24]

Hup a significantly enlarges the number of neurite-bearing cells and up-regulates of P75 low-affinity NGF receptor and NGF markedly.[25,26] For peroxide induces injuries, Hup a is able to mediate the NGF and TrkA receptor to produce neuroprotective actions. Hup a may particularly activate the MAP/ERK kinase pathway to provide protection for SH-SY5Y cells.[26] The neuroprotective effect of Hup a may also be partially modulated signal-regulated kinases1/2 (Erk1/2) phosphorylation on APP processing.[27] [-]-Hup a has numerous neuroprotective properties and rapidly passes blood-brain barriers.[28]

Hup a acts to oppose glutamate-induced cell death and organophosphate (OP) intoxication.[29] In addition, Hup a has neuroprotective effects against Abeta toxicity and markedly enhances GSH-Px and CAT activities and prolongs the cell survival.[30] Hup a improves the abnormal free radicals while dramatically lowers the levels of malondialdehyde (MDA), manganese-SOD (Mn-SOD) and MDA activities in elderly male rats.[31]

Hup a shows a protective effect on cell toxicity induced by free radicals and can reduce the pathological damage of oxygen free radicals.[32,33] Being able to reduce calcium glutamate-induced mobilization, Hup a can be a potent for cholinergic neurons impaired glutamatergic functions.[34] The cell death probably is a factor leading to AD.[35]

The mechanism of Hup a markedly preventing cell death includes renewing Bcl-2 level and attenuating over-expression of Bax and p53 induced by H2O2.[36] Hup a can inhibit ROS formation induced by Abeta 25-35 and the activities of caspase-3, thus protecting neurons from apoptosis induced by Abeta 25-35.[37] By inhibiting the mitochondria-caspase pathway directly and indirectly, Hup a improves neuronal survival markedly and depresses apoptosis.[38] After acute intracerebral hemorrhage, Hup a exhibits protective effects through decreasing apoptosis and mitochondrial injuries, inhibiting cytochrome C translocation and caspase-3 activities.[39] Hup a improves posttrauma motor performance and locomotor abilities while decreases the number of apoptotic cells.[40] Through activating relative signaling pathways, Hup a alleviates oxidative glutamate toxicity in hippocampal HT22 cells.[41] It protects neural stem cells from death induced by Aβ in a co-culture system of neural stem cells and microglia.[42] Through pregnane X receptor-mediated pathways, Hup a enhances the expression induced by CYP3A4.[43] Hup a ameliorates cognitive decline via modulating escape latency, neuronal damage, plasma glucose levels, mean path length, AChE, and MDA level as well as expressions of relative genes in hippocampus and cerebral cortex.[44] Showing inhibition effect on the formation of oxygen species and caspase-3 activity induced by abeta-35, Hup a protects neurons from death caused by beta 25-35.[37] Besides, it significantly enhances the proliferation of cells in dentate gyrus of hippocampus in adult mice and increases the remaining newborn cells.[45] By means of reducing the expression of cellular tumor antigen p53 (Trp53) Hup a protects N2a cells from apoptosis caused by Aβ oligomer.[46] It is also found that inflamm-aging can be suppressed by Hup a via restraining hepatic replicative senescence, NF-κB p65 nuclear translocation, IκBα degradation and inflammatory responses. In addition, Hup a inhibits the damage-associated molecular patterns NF-κB nuclear localization and activation mediated by DAMPs.[47] (Fig. 1).

A new mechanism is found for inhibiting the activity of GSK3α/β and enhancing the level of β-catenin in SH-SY5Y cells which is different from its inhibition on AChE.[48]

4. Effects on the neurotransmitter and the central nervous system

Hup a reverses monoaminergic and cholinergic dysfunctions in dopaminergic, cholinergic, and noradrenergic systems of rat forebrains.[49] Hup a exhibits same effects on cortex and subcortex systemic and local intracerebral administration and it can regulate the levels of DA, NE, and ACh in cortex by penetrating into brains.[50] The results show that the anticholinesterase action of Hup a is stronger than tacrine in cholinergic synapses.[51] In addition, Hup a not only improves learning and memory, but also produces beneficial effects through inducing some changes.[52] With donepezil and rivastigmine, Hup a has the 11- and 2-fold dosages increasing mPFC ACh and DA levels.[53] Apart from acting as a selective and reversible AChE inhibitor, Hup a reverses effects regulated through the GABAA receptor.[54] For AD, Hup a can restrain neurodegeneration by blocking the NMDA ion pathway and following Ca^{2+} mobilization.[55] Meanwhile, the expressions of TNF-alpha, IL-6, IL-1beta, and CCL2 in spinal cords can be remarkablely regulated by Hup a. Moreover, via PPARgamma-dependent and nicotine receptor-independent, Hup a inhibits the generation of CCL2.[56]

4.1. To improve the cognitive ability of memory and reduce the damage

Hup a can enhance memory and neuroprotective effects and improve cognitive deficits and daily living activity with AD.[57] Hup a may be protective against hypoxic-ischemic encephalopathy (HIE) caused by the perinatal asphyxia.[58] Hup a is found to be able to improve scopolamine-induced cognitive impairment.[59] The integrity of magnocellularis is pivotal issue, Hup a is beneficial for ameliorating working memory impairment induced by nucleus basalis magnocellularis damage.[60] In the radial maze, AF64A impairs spatial working memory task, which can be significantly ameliorated by Hup a.[61] Hup a plays an important role in chronic treatment as well.[62] Hup a shows treating effects on the memory deficits in a delayed-response task of young adult monkeys. It reveals that Hup a significantly enhances choice accuracy of four aged monkeys, and the beneficial effects on the performance of delayed-response lasts for a long time.[63] Hup a can decrease the neuronal degeneration triggered by beta-amyloid protein-(1-40) and regulate the expression of proteins relating cell death.[64] Hup a can significantly attenuate memory impairment and neuronal damage in the CA1 region.[65] Be-

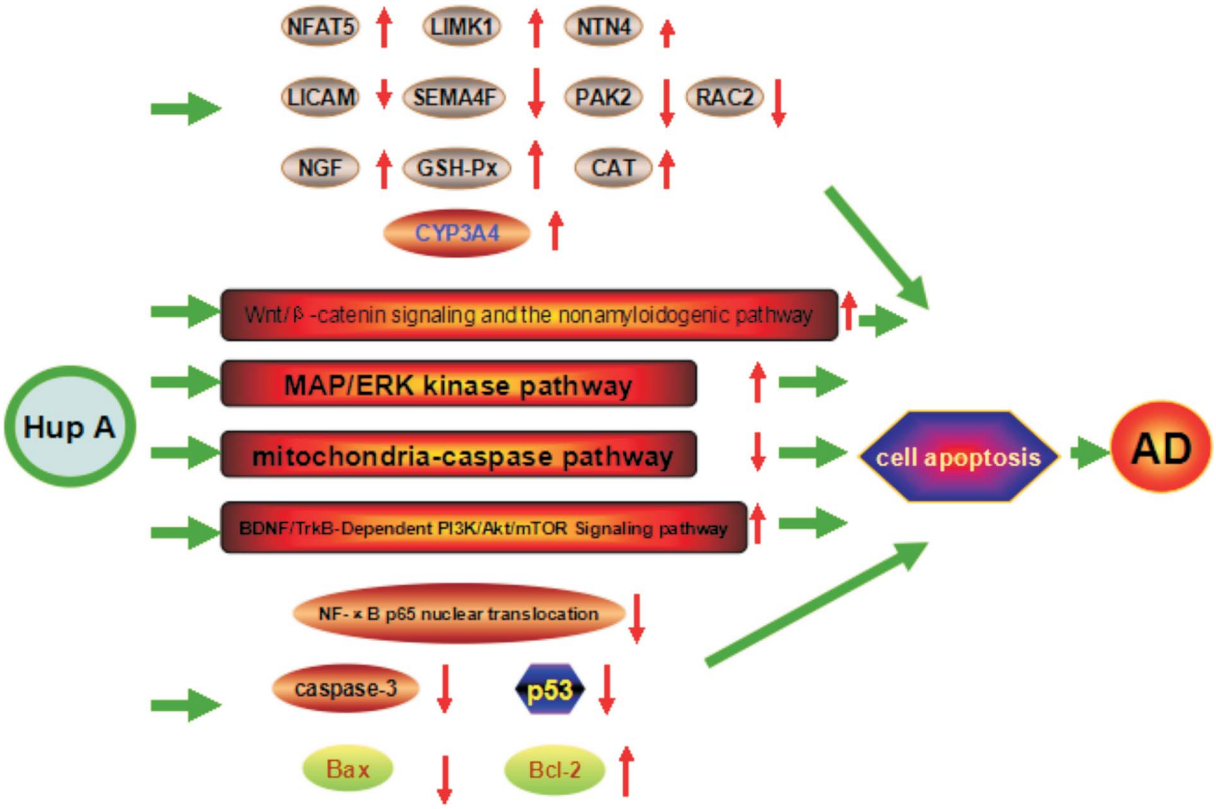

Fig. 1. Mechanism of protecting the cell death.

sides, Hup a might have a remarkable protective effect against HI injuries on neuropathology and behavior of neonates.[66]

Previous research also demonstrates that Hup a is able to inhibit the infusion of beta-amyloid protein-(1-40) into cerebral ventricle of rats and embryonic kidney 293 cells in human. Protein kinase C (PKC) and APP in rats can be up-regulated by Hup a.[67] This indicates that Hup a can attenuate damage and be beneficial for the treatment of HIE in neonatal rats.[66]

By increasing cortical inhibition, Hup a prevents rats from seizures caused by pentylenetetrazole. The activity of Hup a shows that the effect of Hup a is mediated by central nervous systems.[68] Hup a can improve neuroprotection effect on models relating mitochondrial lesion and memory deficits of AβPP/PS1 double transgenic mice. In isolated brain cortical mitochondria, Hup a has an effect on ameliorating oligomeric Aβ1-42-induced ATP reduction and mitochondrial swelling.[69]

Previous study also shows that Hup a can decrease iron level, indicating that it regulates the expression of transferrin-receptor 1 and the absorption of transferrin-bound iron in cultured neurons.[1] In addition, it inhibits the enzymatic activity of respiratory chain complexes, particularly complexes II-III and IV.[69]

Hup a significantly enhances the phosphorylation of p44/p42 MAP kinase which is likely to be obstructed in treating with PD98059 and U0126 (Table 1).[22]

5. Conclusion

AD, as a common form of dementia attacking Chinese and

Table 1
Mechanism of improving the cognitive ability of memory and reducing the damage

	Mechanism	Reference
Hup a	Being protective against HIE caused by the perinatal asphyxia.	Wang LS[58] (2003)
	Enhancing memory and neuroprotective effects and improves cognitive deficits.	Yang G[57] (2013)
	Improved memory impairment by nucleus basalis magnocellularis damage and AF64A.	Xiong ZQ[60] (1998) Zhi QX[61] (1995)
	Enhancing choice accuracy and the beneficial effects on delayed-response performance significantly.	Ye JW[63] (1999)
	Attenuating the memory impairment and neuronal damage in the CA1 region significantly.	Zhou J[65] (2001)
	Protecting against HI injury on behavior and neuropathology in neonates significantly.	Wang LS[66] (2002)
	Inhibiting beta-amyloid protein-(1-40)infusion into the cerebral ventricle and embryonic kidney 293 cells.	Zhang HY[67] (2004)
	Up-regulating APP and PKC in rats.	Zhang HY[67] (2004)
	Attenuating impairment for the treatment of HIE in neonatal rats.	Wang LS[66] (2002)
	Decreasing iron level in the brain.	Huang XT[6] (2014)
	Enhancing the level of a disintegrin and metalloprotease 10.	Huang XT[6] (2014)
	Enhanced the phosphorylation of p44/p42 MAP kinase.	Peng Y[22] (2007)
	Improving neuroprotection effect on models related to mitochondrial lesion and memory deficits in AβPP/PS1 double transgenic mice.	Yang L[69] (2012)
	Ameliorating oligomeric Aβ1-42-induced ATP reduction and mitochondrial swelling.	Yang L[69] (2012)

HIE,hypoxic-ischemic encephalopathy; PKC, protein kinase C; MAP, mitogen-activated protein.

western people, is a complicated brain disease in which various mechanisms are involved. To solve AD, a famous Chinese medicine component, that is, Hup a is reported to exert special effects. This is supposed to be beneficial for the treatment of neurodegenerative illnesses like AD. The research demonstrates that these inspiring clinical and preclinical findings suggest that Hup a is a potentially valuable and novel therapeutic agent for AD.

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Conflict of interest

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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