

Huperzine A reduces neuronal loss and enhances brain expression of nerve growth factor and high-affinity receptor TrkA, and reverses memory and cognitive deficits, in rats with excitotoxic lesion of nucleus basalis magnocellularis

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In our previous study, we demonstrated that Huperzine A (Hup-A), an alkaloid isolated from *Huperzia serrata* (Thunb.) Trevis (Lycopodiaceae), is able to restore cholinergic cortico-hippocampal functional connectivity after bilateral lesion of the nucleus basalis of meynert (NBM) by alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), an in vivo model of Alzheimer's disease (AD). Recently, in addition to its inhibitory effect on acetylcholinesterase, the agent was found to afford neuroprotection in in vitro studies.

As an extension of the previous study, for the first time, we verified whether another pharmacological mechanism is involved in the beneficial profiles of Hup-A on cognitive dysfunction. With this purpose, a set of experiments was planned to evaluate whether Hup-A ability, to prevent neuropathological changes induced by AMPA and subsequent deficit in attention, learning, working and spatial memory observed in rats, could be due to the effects on brain levels of nerve growth factor (NGF) and of its high-affinity tyrosine kinase A receptor (TrkA).

Rats, bilaterally AMPA-lesioned at NBM, were administered with Hup-A (0.5 mg/kg i.p.) daily for two weeks. After that period animals were implanted with neocortical electrode to record electroencephalogram (EEG) and theta rhythm from cortical and hippocampal EEG was monitored, recorded and qualitatively/quantitatively analyzed. Moreover, animals were subjected to object recognition test (ORT) and Morris water maze (MWM) to evaluate their cognitive performance. NGF levels were determined in cerebral cortex and hippocampus by Elisa assay. TrkA receptor expression was evaluated in NBM by Western blotting analysis. Hup-A treatment significantly reduced neuronal loss in NBM and increased NGF levels in both hippocampus and neocortex compared with NBM-lesioned and not treated group and intact controls. Western blotting showed an evident enhancement in TrkA receptor expression in lesioned NBM in comparison with NBM-lesioned and not treated animals and intact controls. Also, Hup-A treatment, as previously demonstrated, was able to restore, in NBM-lesioned rats, the disrupted cortical EEG and HVS activities as well as to reverse deficits in learning and memory in spatial navigation and cognitive capacities in object recognition task. We assume that Hup-A protects against AMPA damage by blocking NMDA-induced excitotoxicity in vivo.

In conclusion, these findings show that Hup-A, after chronic treatment, significantly increases NGF expression and high-affinity receptor TrkA levels in brain. In fact, beyond its main mechanism of action, the neuroprotective activity of Hup-A discloses other potential pharmacological targets and opens a new scenario indicating promising expectation as disease modifying drug to treat Alzheimer's Disease patients.

References

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