Donepezil decreases tau hyperphosphorylation induced by hypothermia in vivo and in vitro

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Tau hyperphosphorylation is one hallmark of Alzheimer's disease (AD). Donepezil is a potent and selective acetylcholinesterase inhibitor developed for the treatment of AD. However, broad therapeutic effects of donepezil cannot be fully explained only by cholinergic hypothesis. Here, we investigated the effects of donepezil on tau hyperphosphorylation in vivo and in vitro. First, we examined whether donepezil reduces tau hyperphosphorylation in the brains of hypothermia mice model induced by anesthesia. Tau phosphorylations detected by anti-phospho tau antibodies, AT8 and PHF1, were significantly increased in anesthetized mice brains. Pretreatment with donepezil for 24 hr inhibited the tau phosphorylation. This was reproduced in vitro model of tau hyperphosphorylation induced by hypothermia using rat primary culture cortical neurons. We also found that the Glycogen synthase kinase-3b (GSK3b) inhibitor decreased in tau phosphorylation in vitro hypothermia model. In vitro kinase assay showed that donepezil suppressed the phosphorylation of purified recombinant tau by GSK3b. These results suggest that donepezil prevents tau hyperphosphorylation induced by hypothermia in vivo and in vitro through GSK3b inhibition.