SYSTEMIC ADMINISTRATION OF EPOTHYLONE-D RECUES MEMORY AND AMELIORATES ALZHEIMER'S DISEASE-LIKE PATHOLOGY IN APP/PS1 MICE

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Aims: Cognitive and memory decline in Alzheimer's disease (AD) patients is highly related to synaptic dysfunction and neuronal loss. Tau hyperphosphorylation destabilizes microtubules leading to axonal transport failure, accumulation of autophagy/vesicular material and the generation of dystrophic neurites, thus contributing to axonal/synaptic dysfunction. In this study, we analyzed the effect of a microtubule-stabilizing drug in the progression of the disease in an APP751SL/PS1M146L transgenic model.

Methods APP/PS1 mice (3 month-old) were weekly treated with 2 mg/kg intraperitoneal injections of Epothilone-D (Epo-D) for 3 months. Vehicle-injected animals were used as controls. For memory performance, animals were tested on the object-recognition tasks, Y-maze and Morris water maze. Levels of Abeta, ubiquitin, AT8 and synaptic markers were analyzed by Western-blot. Hippocampal plaque burden, dystrophic and synaptic loadings were quantified after immunostaining by image analysis.

Results: Epo-D treated mice showed a significant improvement in the performance of hippocampus-associated cognitive tests compared to controls. This memory recovery correlated with a significant reduction in the AD-like hippocampal pathology. Abeta, APP and ubiquitin levels were significantly reduced in treated animals, and a decrease in both the plaque loading and the axonal pathology was also found. Finally, synaptic levels were significantly preserved in treated animals in comparison with controls.

Conclusion: Epo-D treatment promotes synaptic and cognitive improvement, reduces the accumulation of extracellular Abeta and the associated neuritic pathology in the hippocampus of APP/PS1 model. Therefore, microtubule stabilizing drugs could be considered therapeutical candidates to slow down AD progression.

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