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Topic: *Theme A: β-Amyloid Diseases / A2.r. Therapeutic Targets, Mechanisms for Treatment: Other*

MICROTUBULE STABILIZATION REDUCES AMYLOID PATHOLOGY AND IMPROVES SYNAPTIC/MEMORY DEFICITS IN APP/PS1 MICE

Lecture Title:

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Aims: Cognitive decline in Alzheimer's disease (AD) is highly related to synaptic/neuronal loss. Tau hyperphosphorylation destabilizes microtubules leading to axonal transport failure and generation of dystrophic neurites, thus contributing to synaptic dysfunction. The effect of microtubule stabilization on amyloid-β (Aβ) pathology has not been assessed in vivo yet. This study evaluated the effect of the microtubule-stabilizing agent, Epothilone D (EpoD) in the pathology of an amyloidogenic mouse model.
Methods: APP_{751SL}/$PS1_{M146L}$ mice (3-month-old) were treated weekly with intraperitoneal injections of EpoD (2 mg/kg) or vehicle for 3 months. For memory performance, animals were tested on the object-recognition, Y-maze and Morris water maze. Hippocampal proteinopathies were quantified by image analysis after immunostaining. Somatostatin (SOM)-numerical density was calculated by stereology. APPswe-N2a cells were treated with EpoD 100nM for 12/24 hours. Protein levels were analysed by Western/dot-blot.
Results: EpoD-treated mice improved their performance of cognitive tests, while hippocampal phospho-tau and Aβ (especially oligomers) accumulation decreased, together with synaptic/neuritic pathology. Remarkably, EpoD exerted a neuroprotective effect on SOM-interneurons, a highly AD-vulnerable GABAergic subpopulation.
Conclusions: EpoD improved microtubule dynamics and axonal transport in an AD-like context, reducing tau and Aβ accumulation and promoting neuronal and cognitive protection, underlining the cross talk between cytoskeleton pathology and proteinopathy. Therefore, microtubule-stabilizing drugs could be candidates for slowing AD at both tau and Aβ pathologies. Supported by PI18/01557 (to AG) and PI18/01556 (to JV) grants from ISCiii of Spain, co-financed by FEDER funds (European Union), CIBERNED collaborative grant (to AG and JV), and by PPIT.UMA.B1.2017/26 grant (to RSV).