LITHIUM, AS A NEUROPROTECTIVE THERAPY FOR ALZHEIMER'S DISEASE PATHOLOGY, MODIFIES ABETA PLAQUE TOXICITY

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BACKGROUND: Despite the relatively large information about the Alzheimer's disease (AD) pathology, no effective disease-modifying treatment has been yet developed. Lithium, a primary drug to treat bipolar disorder, has been suggested as a potential treatment against AD. In this work we have evaluated whether lithium treatment could ameliorate the neuropathology progression of the transgenic PS1M146L/APPSwe-London mice. Unlike most transgenic animal models, which do not exhibit the neurodegenerative spectrum of disease observed in the patient population, this AD model exhibits a prominent amyloid pathology along with a selective and significant neuronal loss in the hippocampus and entorhinal cortex. Therefore, this model is highly valuable for evaluating the effectiveness of potential neuroprotective therapies for AD.

METHODS: For lithium treatment, PS1/APP mice (3 month old at the beginning of treatment) were fed, ad libitum, with diet supplemented with lithium carbonate (1.2g/kg, Harlan, Spain). The treatment lasts 6 months. After behavioural studies, mice were anesthetized and brains dissected out (hippocampus and cortex). Hemibrains were processed for immunohistochemistry, stereological and image analysis quantification, and the other hemibrains for RT-PCR and Western blot studies.

RESULTS: Our data demonstrate that chronic oral administration of lithium, before the pathology onset, resulted in less toxic plaque formation that significantly ameliorated the degenerative processes and behavioural/memory deficits occurring during disease progression in our PS1/APP model. Specifically, and of great relevance for AD prevention, early lithium intervention was able to arrest neuronal loss in hippocampus and entorhinal cortex of highly vulnerable populations. Besides, lithium reduced the axonal dystrophic pathology, associated to amyloid plaques, by increasing the Abeta compaction. Moreover, a significant lower accumulation of phospho-tau, LC3-II and ubiquitinated proteins was detected. Our study highlights that the switch of plaque quality by lithium could be mediated by astrocyte activation and the release of heat shock proteins, which concentrated in the core of the plaques.

CONCLUSIONS: Our data demonstrate a novel lithium-mediated mechanism capable of altering the course of the disease in an amyloidogenic AD model. This pharmacological in vivo modulation of the extracellular Abeta plaque compaction/toxicity might represent an innovative therapeutic approach for AD.

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