p-242

Friday

Depletion of ChromograninA (CgA) reduces Tau mediated neurodegeneration in vivo

Suborno Jati, Gourisankar Ghosh, Sushil Kumar Mahata, Xu Chen

Alzheimer's disease (AD) and Frontotemporal dementia (FTD) are the most common neurodegenerative disorders that are primarily characterized by the formation of neurofibrillary tangles, and senile plaques composed of hyperphosphorylated Tau and Ab42, respectively. Chromogranin A (CgA) is a prohormone and is known to primarily regulate the secretion system implicated in modulating insulin sensitivity and inflammatory disorders. The coexistence of CgA in the senile neurodegenerative plaques intrigued us to undertake both genetic and biochemical approaches to decipher the role of CgA in the progression of AD and FTD.

We genetically depleted CgA in transgenic PS19 mice (overexpressing human Tau with P301S mutation; hTau+/-). In this study, we took the cortex of PS19 (CgA+/+hTau+/-) and CgA-/-hTau+/- 6-and 9-month-old mice cortex for evaluating the change in Tau hyperphosphorylation, neuroinflammation and catecholamine levels. *Ex vivo* organotypic slice culture (OTSC) was used to examine the Tau (K18) mediated seeding capacity between CgA-/- and CgA+/+ hippocampal slices. We also performed behavioral tests (Open field test, NOR test, MWM test) in a 7-month-old cohort for all two genotypes.

We observed a significantly elevated level of epinephrine both in the plasma and cortex of PS19 mice compared to control. Depletion of CgA substantially reduced Tau hyperphosphorylation in both *in vivo* and *ex vivo* models. In addition, this genetic depletion resulted in noticeably improving the lifespan and behavior of the mice.

CgA exacerbates AD toxicity, and its depletion reduces the disease burden. CgA might be used as a therapeutic target against AD and FTD.

Conflicts of interest

The authors declare no conflict of interest.