DOCTORAL THESIS

Therapeutic effect of cyanines in an alzheimer's disease model in vitro and in vivo

Chen, Chen

Date of Award:
2020

ABSTRACT

Alzheimer’s disease is the most common neurodegenerative disease in the elderly. Senile plaques and nerve cells in the fiber entanglement [neurofibrillary tangle (NFT)] are the significant pathological features. Currently, clinical drugs cannot effectively treat AD and reverse its pathogenesis. Therefore, it is of great importance to research and development of new AD therapy drugs. Carbazole-based cyanine is a type of synthetic small molecule compound that shares a common base with different functional groups; for example, SLOH, SLM, and SLCOOH. They exhibited selective binding to Aβ peptides and showed strong inhibition of Aβ peptide aggregation.

It was found that one of the cyanines, SLOH, could significantly improve the cognitive ability of 3× Tg-AD mice treated for 40 days from the age of 4 months. *In vivo,* SLOH reduced Aβ levels and decreased hyperphosphorylation of tau both in the hippocampus and cortex by downregulating the activity of Akt/GSK3β and protein phosphatase 2A, SLOH can also activate the calcium pathway through activating CAMKII and cAMP-response element-binding (CREB).

SLM significantly improved cognitive deficits in AD mice both in AD mice aged 4 months and 8 months. Both oligomeric Aβ and phosphorylated tau were decreased, and this was due to the activation of autophagic flux.

The other cyanine compound SLCOOH also exhibited significant improvement in the cognitive ability of 4-month 3× Tg-AD mice after two months of treatment. There was significantly reduced Aβ deposition, decreased total tau, and reduced tau hyperphosphorylation by inhibiting the activities of glycogen synthase kinase-3β in 4-month 3× Tg-AD mice. SLCOOH treatment cleared Aβ

and tau by upregulating the autophagy pathway, which inhibited the activity of mTOR/p70S6K. Moreover, SLCOOH structurally restored synapses and spines and regulated the Ca^{2+}/CaMKII/CREB signaling pathway, leading to enhanced synaptic plasticity and cognitive ability in AD mice. Furthermore, we found SLCOOH ameliorated synaptic deficits by downregulating N-methyl-D-aspartate receptors (NMDAR), thereby modulating intercellular calcium ion (Ca^{2+}) loading and upregulating neuronal calcium dependent signaling.

Thus, our results demonstrated that these three carbazole-based cyanines mitigated cognitive decline by targeting Aβ and tau pathology in 3× Tg-AD mice. Those data strongly support that these three carbazole-based cyanines as a potent therapy for AD.

TABLE OF CONTENTS