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MEETING ABSTRACTS

ASSEMBLY OF PRIMA-LINKED FORM OF ACETYLCHOLINESTERASE IN NEURONS: THE ROLE OF ENZYME INHIBITOR ACTING AS CHEMICAL CHAPERON

Karl W. K. Tsim [1,2], Etta Y. L. Liu [1,2], Miranda L. Xu [1,2], Xiang P. Kong [1], Qiyun Wu [1,2], Ran Duan [1,2], Tina T. X. Dong [1,2]
Presenting author: Karl W. K. Tsim

[1] Shenzhen Key Laboratory of Edible and Medicinal Bioresources, SRI, The Hong Kong University of Science and Technology, Shenzhen, China
[2] Division of Life Science, Center for Chinese Medicine, The Hong Kong University of Science and Technology, Hong Kong, China

Acetylcholinesterase (AChE) is anchored onto cell membranes by a transmembrane protein PRiMA (Proline-Rich Membrane Anchor) as a tetrameric globular form that is prominently expressed in vertebrate brain. Several lines of evidence suggest that the dimer formation probably represents an intermediate in the assembly of the tetramer. In addition, the assembly of AChE tetramers with PRiMA requires the presence of a C-terminal "t-peptide" in the AChE catalytic subunit ($AChE_T$). This protein assembly could be affected by chaperons. AChE inhibitors (AChEIs) are the most established treatment strategy for Alzheimer's disease (AD). Many AChEIs are membrane permeable, and thus which could act as chemical chaperons in affecting the protein assembly of PRiMA-linked AChE in the endoplasmic reticulum (ER). In cultured neuroblastoma or cortical neuron, application of AChEIs, including tacrine (Cognex), rivastigmine (Exelon), but not donepezil (Aricept) and galantamine (Razadyne), caused an accumulation of the unfolded AChE being retained in ER fraction: the AChEI-bound enzyme was not able to transport to Golgi/plasma membrane fraction. As a result, the transcripts encoding AChE and PRiMA were decreased by 50% in the AChEI-treated cultures. In parallel, an increase of ubiquitin-associated enzyme degradation was revealed. The treatment of AChEI in the cultures induced the expression of apoptotic markers, e.g. cleaved caspase 3. In parallel, the apoptotic cell number and mitochondrial membrane potential (MMP) were increased in a dose-dependent manner. The AChEI-bound enzyme retained intracellularly could induce a result of ER stress, as indicated by increased expressions of BiP and CHOP in the treated cultures. The AChEI-induced ER stress resulted with an activation of cAMP signaling, which could regulate the expressions of miR132 and miR212. These findings provide guidance for the drug design and discovery in AD based on inhibition of AChE.

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