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Hippocampal Cholinergic Neurostimulating Peptide as a Possible Modulating Factor against Glutamatergic Neuronal Disability by Amyloid Oligomers.

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Abstract

Despite having pathological changes in the brain associated with Alzheimer's disease (AD), some patients have preserved cognitive function. (Snowdon D. The Gerontologist 1997, Stern Y. Lancet Neurol. 2012) A recent epidemiological study has shown that diet, exercise, cognitive training, and vascular risk monitoring interventions may reduce cognitive decline in at-risk elderly people in the general population. (Ngandu T. Lancet 2015) However, the details of molecular mechanisms underlying this cognitive function preservation are still unknown. Previous reports have demonstrated that enriched environments prevent the impairment of hippocampal long-term potentiation (LTP) through β2-adrenergic signals, when LTP is incompletely suppressed by synthetic amyloid-β (Aβ) oligomers. (Li S. Neuron 2013) The cholinergic network from the medial septal nucleus (MSN) is also a main modulating system for hippocampal glutamatergic neural activation through nicotinergic and/or muscarinergic acetylcholine receptors. Previously, we reported the importance of a cholinergic regulator gene in the MSN, hippocampal cholinergic neurostimulating peptide (HCNP). (Ojika K. Progress in Neurobiology 2000) This peptide is formed at the N-terminal region of the 21-kD HCNP precursor protein (HCNP-pp), which is composed of 186 amino acids. (Matsukawa N. Neuroscience 1999) In this study, by using hippocampal sections from mice, we demonstrated that the cholinergic neural activation from the MSN enhanced the glutamatergic neuronal activity during unsaturated LTP but not during saturated LTP. On the other hands synthetic Aβ oligomers suppressed the hippocampal glutamatergic activity in a concentration-dependent manner during unsaturated LTP. Furthermore, overexpressing of HCNP/HCNP-pp, as well as a cholinergic agonist acting through the muscarinic M1 receptor, prevented the suppression of hippocampal glutamatergic neuronal activity induced by synthetic Aβ oligomers. These results suggest that the persisting cholinergic activation might be a potential explanation for the individual differences in cognitive effects of AD pathological changes.