

Neuropeptide as a new diagnostic and therapeutic target for Alzheimer's disease

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The research article reports the new discovery that the native neuropeptide somatostatin (SST) undergoes conformational and functional changes in the presence of copper ions, metal-free amyloid- β (A β), and metal-bound A β (metal-A β), which are pathological factors found in the brains of patients with Alzheimer's disease. These pathological elements induce the self-assembly of SST and, consequently, prevent it from binding to receptors. In the reverse direction, SST notably modifies the aggregation profiles of A β species in the presence of metal ions, attenuating their cytotoxicity and interactions with cell membranes. These overall findings demonstrate a loss of SST's normal functions as a neurotransmitter and a gain in its modulative function against metal-A β under pathological conditions.

Background

Alzheimer's disease (AD) is the most common neurodegenerative disorder, characterized by impairment in overall cognitive abilities such as language proficiency and memory. With the rapid increase in the elderly population and growing life expectancies, the importance of developing treatments has become apparent. However, the mechanism of its onset remains unclear to date. According to the amyloid hypothesis, abnormal deposition of amyloid- β (A β) aggregates is known to cause neuronal cell death. In 2021 and 2023, the U.S. Food and Drug Administration (FDA) conditionally approved the monoclonal antibodies aducanumab and lecanemab, which are known to remove A β aggregates, but issues regarding their efficacy continue to be raised. Since A β aggregates can exist in various forms in the body, understanding the complex mechanisms of AD and developing treatments requires the discovery of new biomarkers. A β aggregates, particularly fibrils, constitute the majority of senile plaques, and recent studies have detected high concentrations of transition metal ions in the plaques of Alzheimer's patients. This suggests the possibility of close interactions between metal ions and A β . Additionally, A β peptides and transition metal ions can interact closely with neurotransmitters at synapses, but there has been limited research on how these pathological factors directly impact the structure and signaling function of neurotransmitters.

Description

Through this work, Prof. Mi Hee Lim and her research group identified a new role related to structural and functional changes in neurotransmitters within the mechanism of the onset of AD (Figure 1). Copper ions [in particular, Cu(II)], A β , and metal-A β complexes, which are considered factors in the onset of AD, induced the self-aggregation of somatostatin. In particular, Cu(II) can bind to both the N-terminus and C-terminus of somatostatin, and through spectroscopies and computational calculations, Prof. Lim's team proposed the coordination structure of copper-somatostatin and the aggregation mechanism of the protein. Upon the binding of Cu(II), it is anticipated

that the N-terminus will fold, leading to an increase in the hydrophobic interaction between phenylalanine residues or the stabilization of hairpin structures, resulting in the formation of parallel oligomers. The somatostatin aggregates generated by Alzheimer's pathological factors were demonstrated to be unable to bind to receptors, interpreted as a loss of their inherent role as neurotransmitters (loss-of-function, Figure 2). Furthermore, depending on the presence of metal ions, somatostatin itself altered the aggregation pathway of A β species and reduced their toxicity. Somatostatin could convert metal-A β aggregates into amorphous forms, hinder their interactions with cell membranes, and thus alleviate cellular toxicity (gain-of-function, Figure 3).

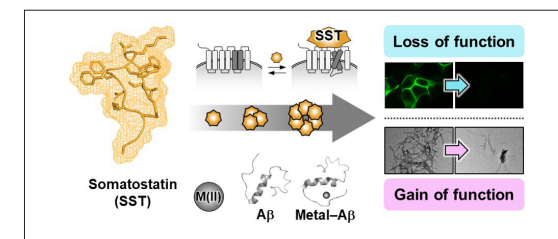


Figure 1. Functional switching of somatostatin (SST) by pathogenic factors associated with AD.

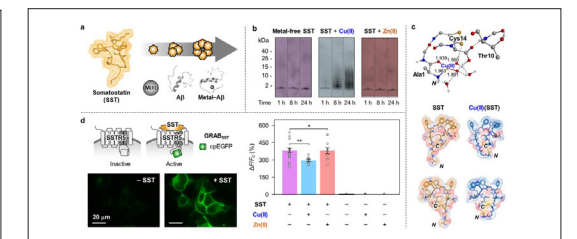
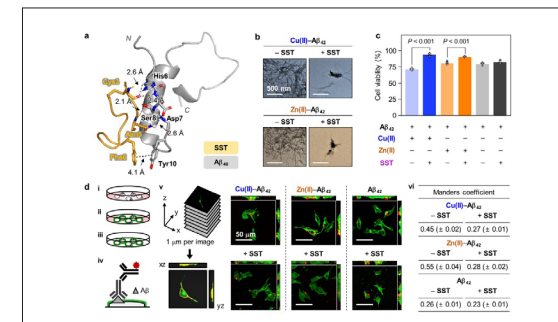


Figure 2. Loss-of-function of SST as a neurotransmitter. a, Schematic representation of SST self-aggregation due to AD pathological factors. b, SST aggregation induced by Cu(II). c, Predicted structure and N-terminal folding of a Cu(II)-SST complex. d, Inhibition of SST receptor binding upon interaction with Cu(II).

Figure 3. New functions of SST under pathogenic conditions (gain-of-function). a, Complexation between SST and A β predicted by docking studies. b, Influence of SST on metal-A β aggregation (forming off-pathway amorphous aggregates). c, Effect of SST on the cytotoxicity induced by metal-A β complexes (diminishing their toxicity). d, Impact of SST to alter the interaction between cell membranes and metal-A β complexes (decreasing their membrane interaction).

Implications

The study proposes a novel role of somatostatin within the mechanism of the AD onset. The significance of this research lies in the fact that it reveals, for the first time, in the dementia context, that amyloidogenic neurotransmitters, such as somatostatin, contribute to the alleviation in neurotoxicity instead of cellular signal transduction. Through this research, clues can be provided for uncovering new biomarkers in the complex dementia network involving A β and metal ions. Considering the annual medical expenses incurred by dementia patients amount to trillions, this study is expected to significantly contribute to early diagnosis, the prevention of the disease, and the reduction of socio-economic burdens. Furthermore, as the first report to elucidate the direct interaction among A β , metal ions, and neurotransmitters within synaptopathy, it serves as a cornerstone for deriving a new paradigm in the development of treatments for neurodegenerative disorders in the future.

Research outcomes

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Media Promotion : TJB News: Pathway Opens for Alzheimer's Treatment with Growth Hormone Inhibiting Hormone

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