

アミロイド β に対する凝集抑制・乖離促進作用を有する短鎖ペプチドのアルツハイマー病治療薬としての可能性

Possibility of short synthetic peptides with activities of suppressing amyloid β aggregation and resolving its aggregated form as therapeutic drugs for Alzheimer's disease

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Lecanemab is a new anti-amyloid antibody being developed as a treatment for Alzheimer's disease. It is expected to delay the progression of the disease by reducing the accumulation of amyloid beta ($A\beta$) in the brain. However, no drug has been developed that can completely eliminate $A\beta$ and improve symptoms. A representative Catalytide, JAL-TA9 (YKGSGFRMI), cleaves $A\beta$ 42 and improves symptoms in an Alzheimer's disease mouse model, suggesting that JAL-TA9 is a promising candidate for treating Alzheimer's disease by effectively eliminating $A\beta$. The catalytic center of JAL-TA9 is GSGFR [1]. To identify better Catalytides for Alzheimer's treatment, we analyzed the structure-activity relationship of 21 point-mutated GSGFR derivatives [2]. In this process, we discovered two peptides, GSGFK and GSGNR, that not only inhibit $A\beta$ 25-35 aggregation but also dissolve aggregated $A\beta$ 25-35 [3]. Intracerebroventricular administration of GSGFK protected mice against $A\beta$ 25-35-induced short-term memory deficits and promoted microglial phagocytic activity. Like Lecanemab, GSGFK targets $A\beta$, but it has advantages such as safety, administration method, and cost. In this talk, we will discuss the potential of GSGFK as a therapeutic candidate for Alzheimer's disease.

[1] Nakamura et al., *Integr Mol Med*, 6, 2 (2019)

[2] Nakamura *et al.*, *biomolecules*, 12(12), 1766 (2022)

[3] Nakamura *et al.*, *Alzheimer's Res Ther*, 15, 83 (2023)