Γ-Secretase Modulator GSM-1 Directly Targets the N-Terminal Fragment of PreSelinin 1

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Aβ is proteolytically derived from amyloid precursor protein by sequential cleavages by β- and γ-secretases. However, treatment with γ-secretase inhibitors (GSIs) causes severe adverse effects by inhibition of Notch cleavage, another substrate for the γ-secretase. Thus, γ-secretase modulators (GSMs) that selectively regulate the generation of the most aggregable Aβ species ending at 42nd residue (Aβ42) without affecting Notch signaling, are currently highlighted, although the target molecules and mode of actions of GSMs still remain controversial. Here, we identified the molecular target of GSM-1, one of the orally-active potent Aβ42-lowering GSMs, using a chemical biology approach. We synthesized a GSM-1-based novel photoprobe GSM-1-BpB equipped with photoactivatable benzophenone and biotin moieties for target purification. After photolysis, the N-terminal fragment (NTF) of presenilin 1 (PS1), the catalytic subunit of γ-secretase, was specifically precipitated by GSM-1-BpB. Furthermore, we observed the direct biotinylation of PS1 NTF by GSM-1-BpB, suggesting that PS1 is the \textit{bona fide} molecular target of GSM-1. GSM-1 treatment decreased the binding of helical peptide-based and transition-state analogue-type GSIs to PS1 in cross-competition experiments. These data suggest that GSM-1 allosterically caused conformational changes in the initial substrate binding site as well as the catalytic pocket within PS1. Our results indicate that GSM-1 directly targets PS1 NTF in a unique mode of action that is distinct from those of conventional GSIs.