Supporting Information

Molecular Mechanism of Secreted Amyloid-ß Precursor Protein in Binding and Modulating $GABA_BR1a$

Mei Feng[1,5#], Yi Song[1#], Serena H. Chen[2], Yuanzhao Zhang[3], and Ruhong Zhou[1,4*]

[1] Institute of Quantitative Biology, College of Life Sciences, and Department of Physics, Zhejiang University, Hangzhou 310027, China

[2] Computational Sciences and Engineering Division, Oak Ridge National Laboratory, Oak Ridge, TN 37830, United States

[3] Center for Applied Mathematics, Cornell University, Ithaca, NY 14583, United States

[4] Department of Chemistry, Columbia University, New York, NY 10027, United States

[5] Lanzhou Center for Theoretical Physics, Key Laboratory of Theoretical Physics of Gansu Province, Lanzhou University, Lanzhou, Gansu 730000, China

# These authors contributed equally

* To whom correspondence should be addressed. E-mail: rhzhou@zju.edu.cn

As an additional step, we also analyzed the effect of the remaining 8 residues of the APP 17-mer peptide in the APP 17-mer peptide - sushi 1 domain binding. Taking Asp11 as an example, which has a low contact probability and contact area ratio with the sushi 1 domain, but the averaged interaction energy with the sushi1 domain is not that weak. We found that Asp11 did not form stable contact with the sushi 1 domain. The residues in sushi 1 that have a relatively high contact probability to Asp11 are Arg25 and Lys29, even though Asp11 does not contact with any of them in most of the time either (Fig. S2A, 77.7%). Only occasionally, Asp11 contacts with either Arg25 (Fig. S2B, 10.9%) or Lys29 (Fig. S2C, 9.3%) through "salt-bridge-like" short-range electrostatic interactions. Even less frequently, it contacts with both Arg25 and Lys29 (Fig. S2D, 2.1%) and forms salt-bridges with both Arg25 and Lys29 residues. Therefore, the binding to sushi 1 is well preserved through the first 9 residues in the

APP 17-mer peptide.

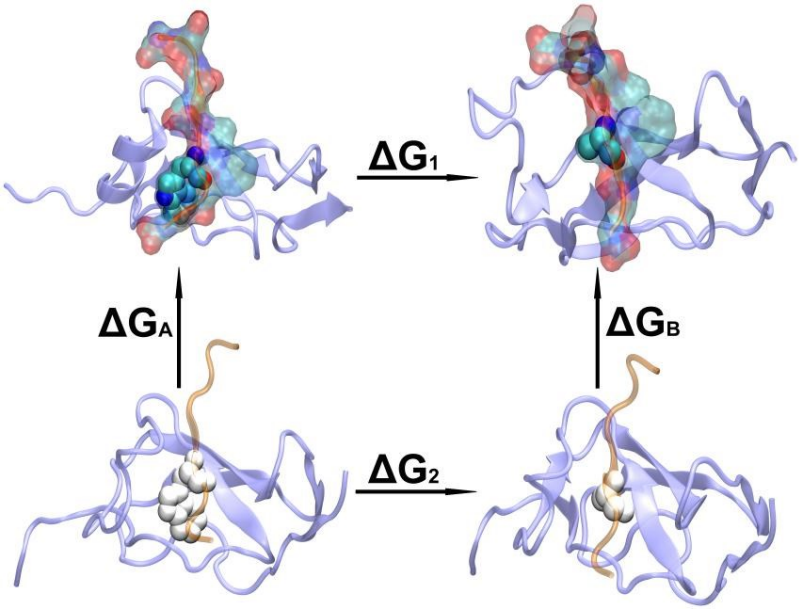

Figure S1. Illustration of the thermodynamic cycle for computing ΔΔG of mutating a residue from Trp to Ala (W6A). The definitions of each ΔG component are listed in the main text.

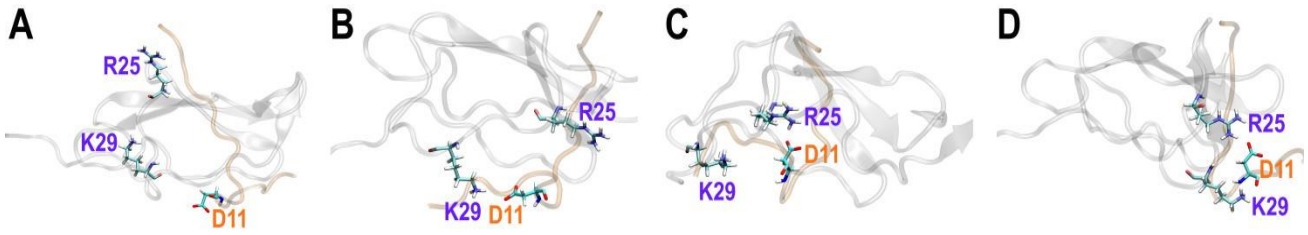

Figure S2. Detailed view of the interaction between Asp11 (D11 in the APP 17-mer) and sushi 1 domain. D11 does not contact with any residues (A), contacts with either R25 (B) or K29 (C), and contacts with both R25 and D29 (D). APP 17-mer and sushi 1 domain are represented by Newcartoon, and the contact residues are rendered with sticks.

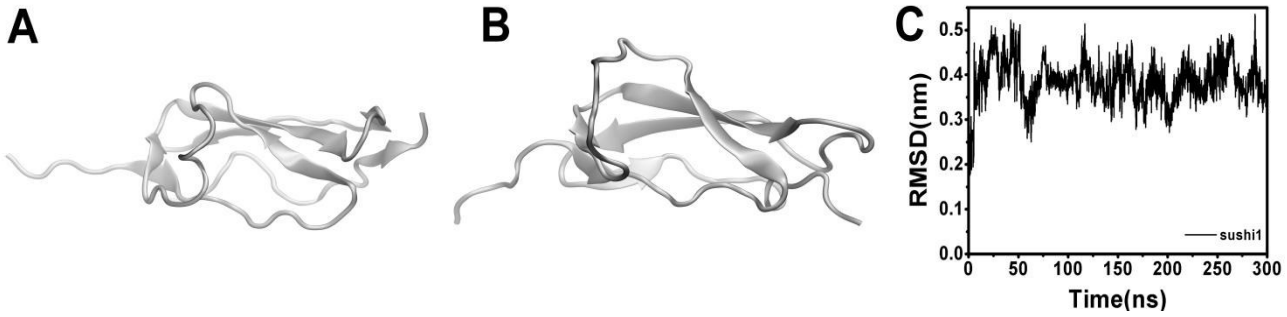

Figure S3. Initial conformation (A), final conformation (B) and RMSD (C) of sushi1 in the system containing the sushi1 domain alone.

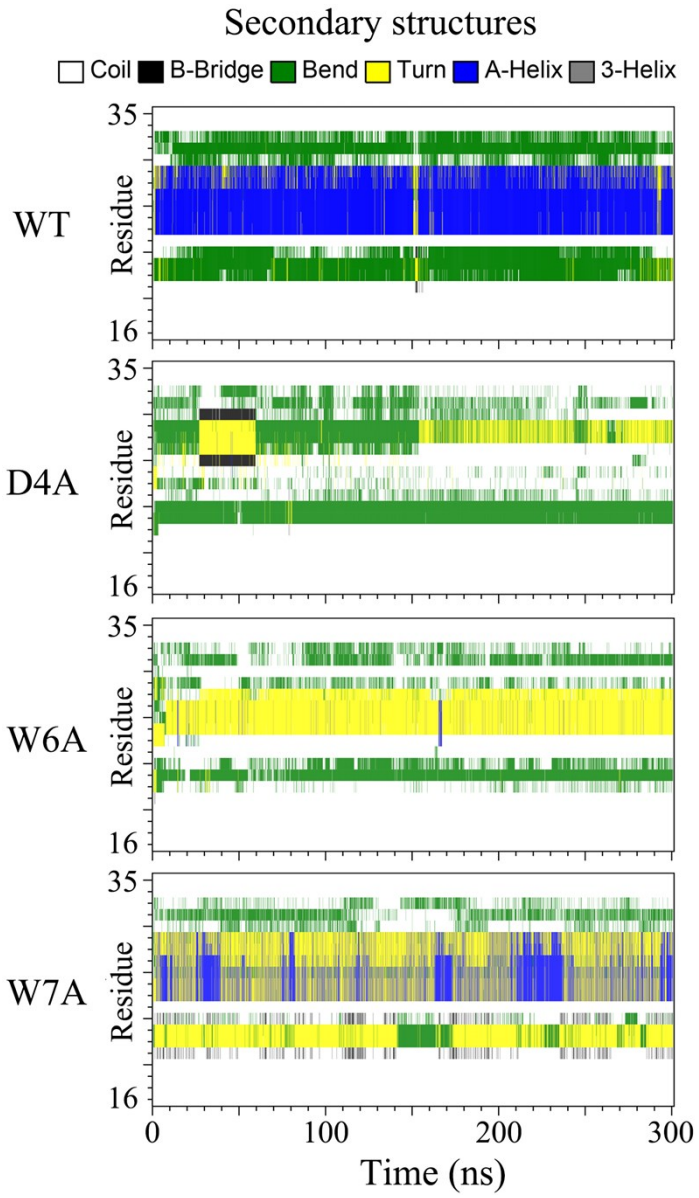

Figure S4. The secondary structure of the shallow binding groove region of sushi 1 domain changes over total simulation time for WT and mutants of APP 9-mer.

We investigated the shallow binding groove region of sushi1 domain (i.e. residues Gly 16 to Pro 35), the secondary structure plots generated with the DSSP program[1] for WT and mutations D4A, W6A, and W7A of APP 9-mer.

References

1. Kabsch W, Sander C (1983) Dictionary of protein secondary structure: pattern recognition of hydrogen-bonded and geometrical features. *Biopolymers* 22 (12):2577-2637.