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Supplementary Material

Understanding the Mechanism of Activation/Deactivation of GLP-1R via Accelerated Molecular Dynamics Simulation

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Methods

In order to clarify whether structure differences have effects on the communication pathways in Fig. 5, we constructed the 3rd system from the 5vai structure with G-protein, nanobody, ligand and N-terminal were deleted (denotes as GLP-1R/active state-without N terminal). The System preparation was performed same as the other two models (GLP-1R/inactive state and active state), and the obtained system contains approximately 80,000 atoms with the box size of 81 Å × 81Å × 134 Å(see Fig. S1). Then the same molecular dynamics simulation were carried out and the trajectories of 200 ns conventional MD (cMD) and 1μs accelerated MD (aMD) simulations were saved for analysis.

Discussion

The RMSD values of the three systems were depicted by Fig. S2. Comparative molecular dynamics simulations indicate that the RMSD values of GLP-1R/active state-without N terminal system is higher than the inactive state system, it may be due to that the conformation transition is much more significantly during the deactivation process of GLP-1R/active state-without N terminal system. Due to the flexibility of N terminal, RMSD values of the active state is higher than the removal of the N terminal system, and the values decreased significantly when the removal of the N terminal. As shown in Fig. S3, the overlay of the first and last frames of the accelerated molecular dynamics (aMD) simulation for GLP-1R/ active state without-N terminal and the first frame of the GLP-1R/ inactive sate system indicates that TM6 undergoes significant inward movement during 1 μs aMD simulation and GLP-1R/active state-without N terminal system is closed to the GLP-1R/ inactive state system. It may be assumed that the removal of N-terminal in the active state may induce or accelerate the deactivation process, this provides a further support for the role of N-terminal in the receptor conformational transition process.

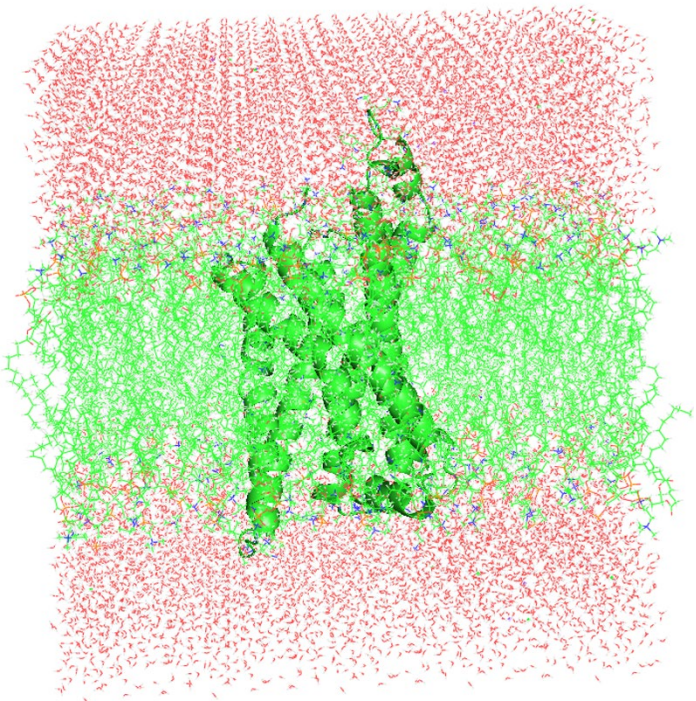

Fig. S1. The GLP-1R/ active state-without N terminal model shown in ribbon form with the hydrophobic bilayer boundaries and water box.

Table S1 The High Frequency Value and High Frequency Path of the three systems.

System	Res1	Res2	High Frequency Value(100%)	High Frequency Path
Active state	A:N240	A:Y250	84.2	A:N240=>A:S186=>A:W243=>A:I179=>A:Y250
Inactive state	A:N240	A:S352	38.85	A:N240=>A:F187=>A:L183=>A:Y402=>A:S352
Active state-without N terminal.	A:N240	A:L254	30.49	A:N240=>A:S186=>A:W243=>A:I179=>A:Y250 =>A:L254

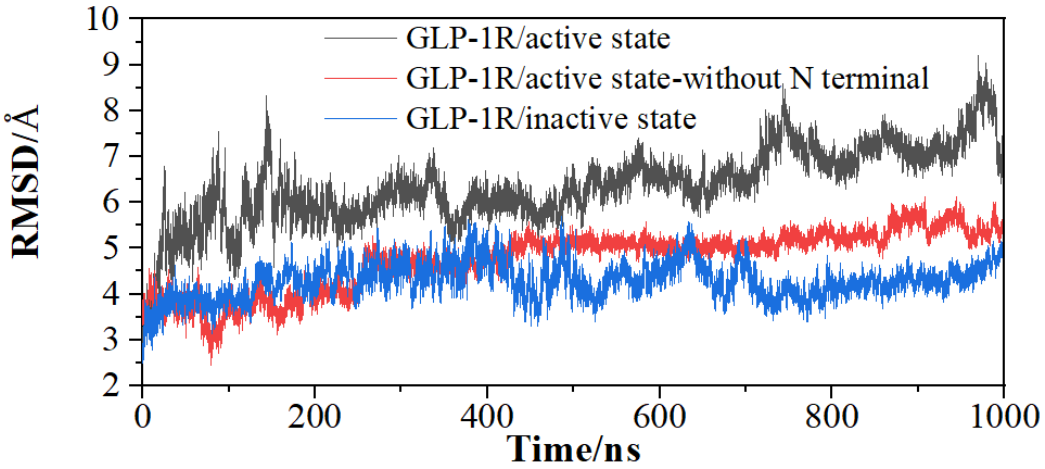

Fig. S2. The RMSD curves of GLP-1R/active state, GLP-1R/inactive state and GLP-1R/active state-without N terminal.

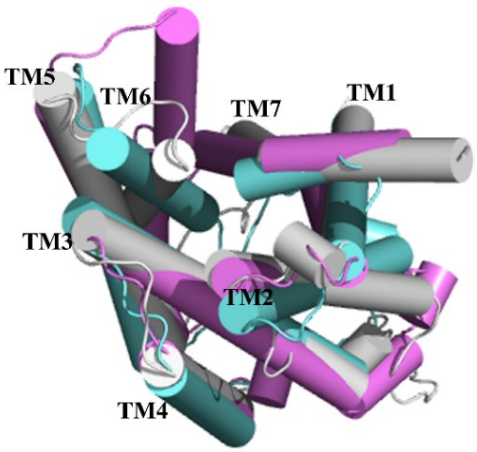

Fig. S3. The overlay of the first and last frames of the accelerated molecular dynamics (aMD) simulation for GLP-1R/active state-without N terminal and the first frame of the GLP-1R/ inactive state system. The conformations were colored by: magenta-first frame of GLP-1R/active state-without N terminal, grey-last frame of GLP-1R/active state-without N terminal, cyan- first frame of GLP-1R/inactive state.

The RMSDs for the cMD simulations of GLP-1R show a relatively stable curve (Fig. S4), which means that 200ns simulation is enough for the system to equilibrate fully.

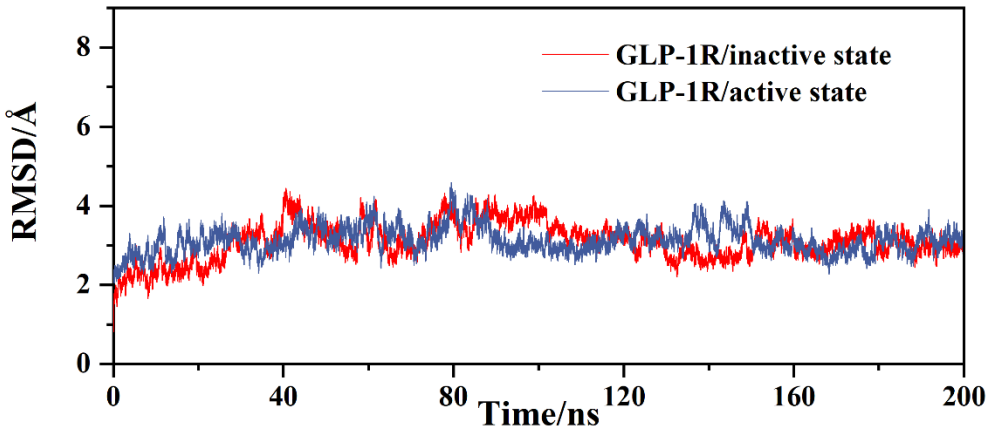

Fig. S4. The RMSD curves of GLP-1R/active state and GLP-1R/inactive state for the cMD simulations.