Scrutiny of the mechanism of β-amyloid protein captures HSV-2 to protect the brain infection

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Abstract. Alzheimer's disease (AD) is an age-related neurodegenerative disorder. β-amyloid protein (Aβ) is the key protein which involved in AD. But the physiological function of Aβ is needed to be investigated. Many experimental studies have shown that Aβ could bind to glycoproteins D (gD) on the surface of the herpes virus. However the mechanism is still unclear. In the present study, we elucidate the molecular mechanism of the interaction between Aβ and gD of herpes simplex virus type 2 (HSV-2) by molecular docking and molecular dynamics simulation. Molecular dynamics simulations displayed that Aβ could stably bind to the HSV-2 gD owing to the presence of several interactions. Analysis binding free energy by molecular mechanics Poisson–Boltzmann surface area (MM–PBSA) method revealed that hot residues including Glu3, Glu11, Glu22 and Ala42 of $A\beta_{1\text{-}42}$ were involved in binding with HSV-2 gD. Thus, the HSV-2 gD can be entrapped by Aβ which will be utilized for prevent and therapy of AD in future.

1 Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disease [1]. β-amyloid protein (Aβ) deposition in the brain is considered as the main neuropathology characteristics of AD. Biological characteristics of Aβ were still need to be investigated, to clarify the pathophysiology effect in AD. Recently, the deposition of Aβ may be considered as a protective innate immune response to infection [2, 3]. Therefore, the aggregation of misfolded of Aβ may be caused by excessive activation of the immune response in the brain.

It was found that viral infections may be a risk factor for neurodegenerative diseases, and many studies have revealed the link between herpes simplex virus type 2 (HSV-2) and AD [4, 5]. HSV-2 is a neurotropic virus, which can establish a latent infection in trigeminal ganglia at infected individuals [5].

In this study, we docked HSV-2 extracellular glycoprotein D with Aβ through molecular docking. Then, the molecular mechanism of Aβ capturing herpes virus was deeply understood by molecular dynamics simulation combined with binding free energy. The present work illustrates the innate immune roles of Aβ at the molecular-level.

2 Computational details

2.1. Protein-protein docking

The docking was performed using Discovery Studio 2016. The ZDOCK and RDOCK programs were used to dock the HSV-2 gD and Aβ. The solution structure of AD full-length Aβ peptide (1–42) (PDB ID: 1IYT) and the crystal structure of HSV-2 gD (PDB ID: 4MYW) were retrieved from the protein data bank (http://www.rcsb.org).

2.2. Molecular dynamics (MD) simulations

Each of the complex systems was performed MD simulations using the GROMACS 5.1.5 software with the GROMOS96 54a7 force field [6]. The best docked complex was solvated in a cubic box with simple point charge (SPC) water model [7]. Energy minimization of the system was used the steepest descent and conjugate gradient method until convergence. In order to equilibrate the system, a position restrained dynamics simulation (NVT and NPT) was performed before sampling [8, 9]. Finally, the 30ns explicit MD simulations were performed using V-rescale thermostat and Parrinello-Rahman barostat with an integration step of 2 fs [9, 10]. Initial velocities of the atoms were assigned randomly from a Maxwell distribution using random seeds (gen_vel = yes, gen_seed = -1).

2.3. Evaluation of binding free energy

The binding free energies were evaluated using molecular mechanics Poisson–Boltzmann surface area (MM–PBSA) by the g_mmpbsa tool of GROMACS [11]. A total of 100 frames were extracted at 100ps interval from the last 10ns (20-30ns) MD trajectory for each system regularly. Based on MM–PBSA method, the binding free energies (ΔG_{bind}) was calculated as:

$$\Delta G_{\text{bind}} = \Delta G_{\text{complex}} - [\Delta G_{\text{protein}} + \Delta G_{\text{ligand}}] \quad (1)$$

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3 Results

3.1. The prediction of binding mode and key interactions of HSV-2 gD–Aβ1-42 compex

In the present study, protein-protein docking analysis was performed to elucidate the binding mode between HSV-2 gD and $A\beta_{1-42}$. The ZDOCK Score and *E*_ROCK of the complex was noted to Table 1. The best pose with -16.55 kcal·mol^{-1} *E*_RDOCK value was selected for interaction network analysis. The 2D interaction map formed by the best-docked pose which is evaluated by the lowest E_RDOCK (Figure 1). The interaction between receptor and ligand are mainly hydrogen bonds, attractive charges, and alkyl interaction.

Table 1. Protein-protein docking analysis of best-docked complex.

ZDOCK Score	*E*_RDOCK (kcal·mol^{-1})	Residues participating in intermolecular hydrogen bonds with $A\beta_{1-42}$		
		Residue	Atoms[a]	Distance(nm)
13.04	-16.55	Arg5	HN: O	2.9483
		Asp7	HN: OD2	1.9998
		Glu11	HE21: OE1	2.2587
		Gln15	HE21: O	2.0547
		Gln15	HE21: O	2.2941
		Gln15	HE22: OE1	2.5299
		Gln15	HD22: OE1	2.6054
		Gln15	HN: OE1	2.7645
		Lys16	HZ3: OD1	1.9391
		Asp23	HH: OD1	2.8471
		Asp23	HH: O	2.0213
		Asn27	HD21: OH	2.0487

[a]The atoms on the left side are complexes residues and atoms on right side are $A\beta_{1-42}$ residues.

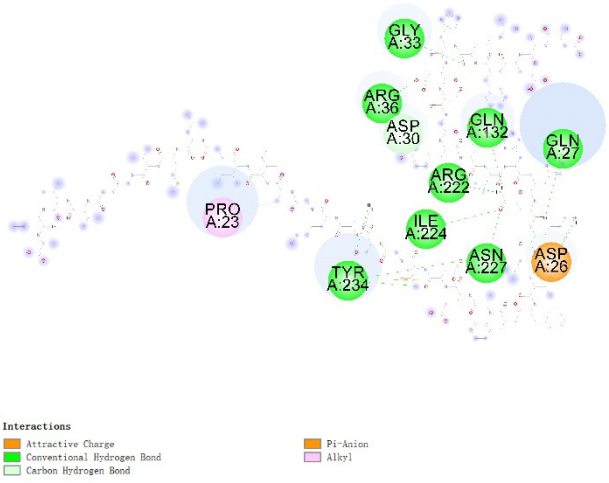

Figure 1. The 2D interaction map of best-docked complex.

As shown in Table 1, the Arg5, Asp7, Glu11, Gln15, Lys16, Asp23, and Asn27 residues of HSV-2 gD forms twelve hydrogen bonds with $A\beta_{1-42}$. The conformation of complexes also stabilized by attractive charges electrostatic interaction and alkyl hydrophobic interaction. Compared the count of typical hydrogen bonds, the larger amount, the better the binding affinity between the protein and the ligand [12]. The docking analysis indicated that Aβ could bind to the envelope of HSV-2 gD. These results illustrate the Aβ binding mechanism and further confirm that Aβ has a high affinity to herpesvirus envelope proteins.

3.2. Analysis of structural stability of the complex by potential energy, RMSD, RMSF, Rg

The MD simulation approach was used to analyze conformational and detect molecule binding model [13]. As shown in Figure 2(up), the average value of potential energy was -309,500 kcal·mol^{-1}, which remained stable throughout the simulation run. The analysis of MD trajectories showed that the root mean square deviation (RMSD) of the complex started to stabilize after ~10 ns with RMSD values varying between 0.5 ± 0.05 nm. (Figure 2(down)).

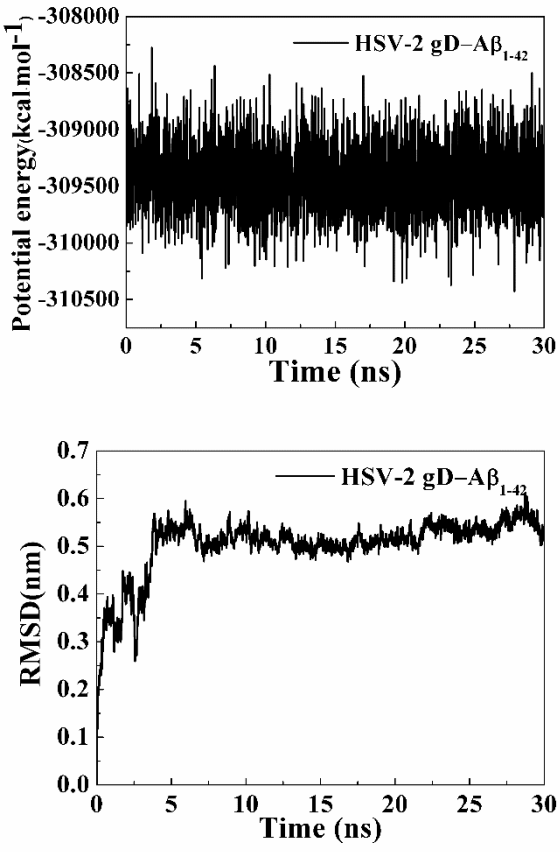

Figure 2. The potential energy (up) and backbone RMSD (down) over 30 ns molecular dynamics simulation.

Similarly, the radius of gyration (Rg) of complexes started to stabilize with a fluctuation after 10 ns, that value reduction indicated enhanced system stability (Figure 3(up)). The Cα root mean square fluctuation (RMSF) of each residue for $A\beta_{1-42}$ was shown in Figure 3(down). The value of RMSF had significant difference in His14, Gln15, Phe19, Glu 22, and Gly 25 residues. These fluctuations

highlighted that the central hydrophobic region $A\beta_{1-42}$ played important roles in binding to herpesvirus envelope glycoproteins. These results testify that the complexes reach a more compact state with the simulation.

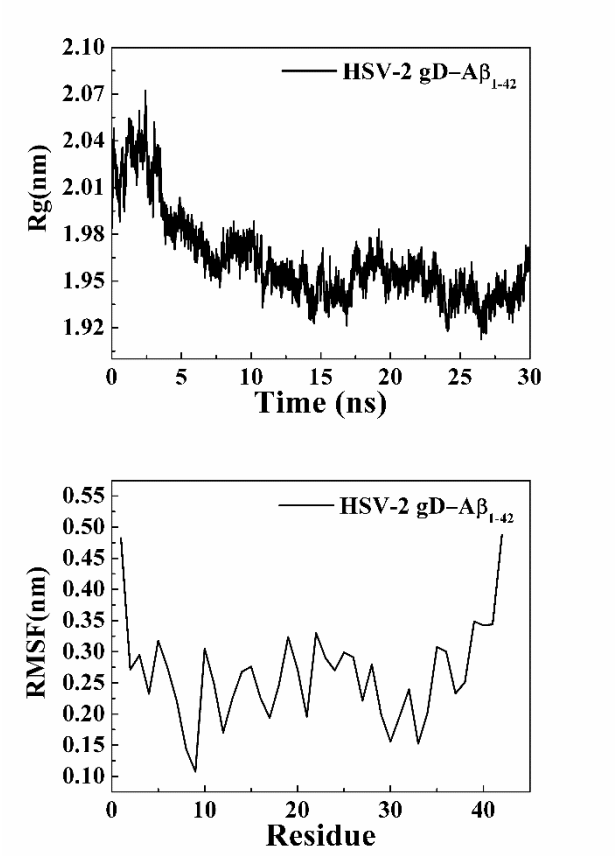

Figure 3. The RMSF (up) and Rg (down) plotted as a function of simulation.

3.3. Binding mode analysis

To investigate the contribution of microscopic element relation to sustaining the binding affinity between the receptor and the ligand, the number of hydrogen bonds formed between complexes were evaluated for complexes during the simulation. The complexes obtained the number of hydrogen bonds 7 to 10 in the simulation period (Figure 4(up)). The formation of hydrogen bonds for complex was the major factor in maintaining molecular affinity and stability. The analysis of hydrogen bonds identified that $A\beta_{1-42}$ strongly and stably bind to herpesviridae.

To further evaluate the conformational stability, the minimum distance between the receptor and the ligand were depicted in Figure 4(down). The minimum distance between complexes were detected as ~0.17 nm. The minimum distance kept in a stable tendency during the 30ns MD simulation. It showed that the complexes maintained the conformational stability throughout the simulation period.

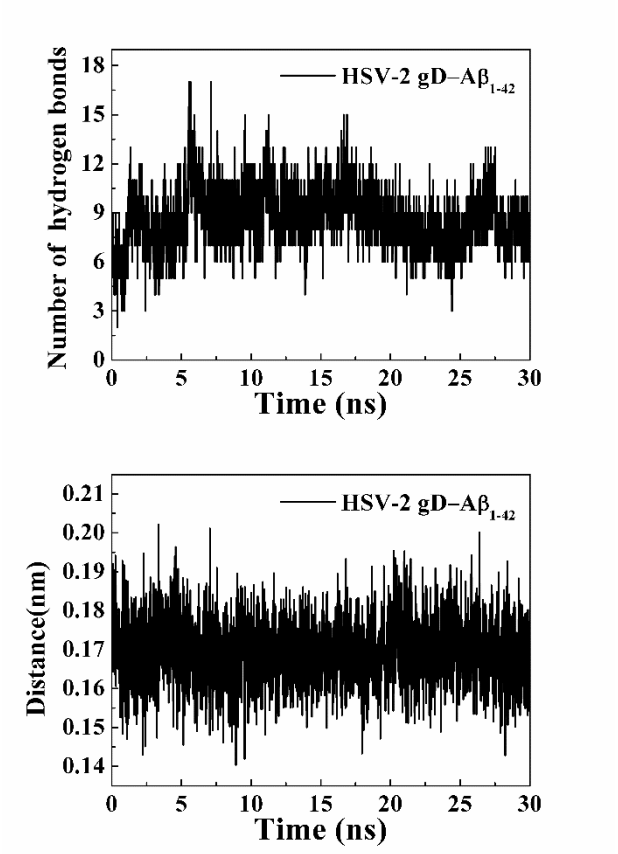

Figure 4. The number of hydrogen bonds (up) and the minimum distance (down) of complex.

3.4. Analysis the molecular interaction between HSV-1 and Aβ by MM–PBSA

To provide deeper insight into the relationship between the binding affinity and the contribution of the energetic parameters, the binding free energy was calculated via the MM–PBSA method. As listed in Table 2, the binding free energy was -132.16 kcal·mol^{-1}, which indicated the spontaneous binding between HSV-2 gD and $A\beta_{1-42}$. Detailed analysis of the energetic components of the binding free energy indicated that the van der Waals (ΔE_{vdw}) interaction and electrostatic (ΔE_{elec}) interaction are the favorable components of the binding affinity. However, the solvation energy (ΔG_{solv}) was averse to the binding mode. The results suggest that the hydrogen bonds and salt bridge interactions play a critical role in the stability of HSV-2 gD–$A\beta_{1-42}$ complex.

Table 2. The binding free energy (kcal·mol^{-1}) between complexes.

Energy terms (kcal·mol^{-1})	ΔE_{vdw}	ΔE_{elec}	ΔE_{MM}[a]	ΔG_{ps}	ΔG_{nps}	ΔG_{solv}[b]	ΔG_{bind}[c]
complex	-95.64	-230.89	-326.53	206.66	-12.29	194.37	-132.16

[a]$\Delta E_{MM} = \Delta E_{vdw} + \Delta E_{elec}$

[b]$\Delta G_{solv} = \Delta G_{ps} + \Delta G_{nps}$

[c]$\Delta G_{bind} = \Delta E_{MM} + \Delta G_{solv}$

In addition, the detailed energetic estimation of the interactions between each residue of Aβ was carried out

by binding energy decomposition using MM–PBSA method. The origins of the binding affinity between HSV-2 gD and Aβ were shown in Figure 5. The interaction energy less than -2.5 kcal·mol^{-1} of residue with the receptor were considered to be important in binding [14]. As shown in Figure 5, the residues (Glu3, Asp7, Glu11, Val12, Phe19, Glu22, Asp23, Val24, Leu34, Ile41, Ala42) dominated contribution maximum towards binding free energy in the complex.

The results indicated that the high binding affinity of residues for $A\beta_{1-42}$ N-terminal, C-terminal, and central hydrophobic region with herpesvirus envelope proteins.

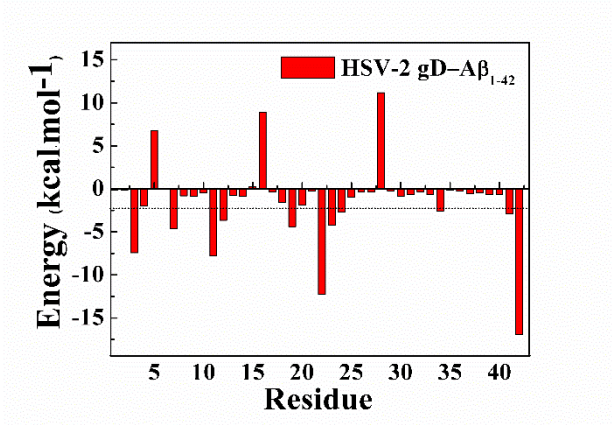

Figure 5. The binding free energy (kcal·mol^{-1}) contribution of each residue of Aβ in complex.

4 Conclusion

In the present study, molecular mechanism between HSV-2 gD and $A\beta_{1-42}$ as well as the structural stability of the complex were explored using protein-protein docking and molecular dynamics in the explicit solvent. The main perceptions gained were as follows: (i) $A\beta_{1-42}$ bind to HSV-2 gD for the formation of a stable complex. (ii) The binding of Aβ with HSV-2 gD tended to occur spontaneously, mainly through hydrogen bonds, salt bridges and hydrophobic interactions. (iii) The MM–PBSA highlighted non-bonded van der Waals and electrostatic interactions played a crucial role in the stable binding of Aβ to the herpes virus glycoprotein. (iv) The hydrophobic effect had a great contribution to the combination of the herpesvirus-Aβ complex, which hotspot residues between Aβ and herpesvirus envelope glycoprotein were Glu3, Asp7, Glu11, Val12, Phe19, Glu22, Asp23, Val24, Leu34, Ile41, Ala42 of Aβ, and other hydrophobic residues. The elaboration of the interaction mechanism between Aβ and herpesvirus envelope proteins reveals the protective effect of Aβ in the central nervous system.

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