On Hydrogen bonding of ATP-IDE interactions uncovered by quantum mechanics/molecular mechanics (QM/MM) calculation and molecular dynamic (MD) simulations

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Structured abstract

Background: The insulin-degrading enzyme (IDE) plays a significant role in the degradation of the amyloid beta (Aβ), a peptide found in regions of the brain of patients with early Alzheimer's disease (AD). Adenosine triphosphate (ATP) allosterically regulates the Aβ-degrading activity of IDE. Hydrogen bonding interactions between ATP-IDE including thermostabilities/flexibilities of IDE residues, at the allosteric site of IDE, are essential for drug design. The hydrogen-bonding interactions of ATP and IDE including the thermostabilities/flexibilities of IDE residues have not yet been systematically understood. The present study elucidates the hydrogen bonding of ATP-IDE interactions and the thermostabilities/flexibilities of the IDE residues.

Methods: This study applies the quantum mechanics/molecular mechanics calculation method (QM/MM) to the proposed computational model for exploring the hydrogen-bonding interactions of ATP with IDE. Molecular dynamic (MD) simulations are performed at different heat-shock temperatures for identifying flexible and stable residues of IDE.

Results: The proposed computational model predicts QM/MM minimised structures. Subsequently, it reveals the IDE residues with high binding affinity. Considering RMSF values during the MD simulations at the heat-stress, it indicates the thermostable residues of IDE and IDE residues with flexibilities with compromised thermostabilities.

Conclusions: The present study sheds light on the phenomenon of biological recognition and interactions at the ATP-binding domain within the IDE which has important implications for pharmacological drug design. The proposed computational model may facilitate the development of allosteric IDE activators/inhibitors which mimic ATP interactions.

Keywords: hydrogen bonding; QM/MM Calculation method; molecular dynamic simulation, thermostability

Author summary: *ATP acts as an allosteric regulator of IDE in Aβ clearance (the degradation of Aβ). Computational methods for the hydrogen bonding of ATP-IDE interactions and molecular dynamics (MDs) of IDE are essential for the pharmacological drug design against early AD. The computational proposed model, involving QM/MM calculation and MD simulations, is developed to explore the hydrogen bonding of ATP-IDE interactions and MDs of IDE at heat-shock temperatures. Subsequently, the hydrogen bonding interactions between ATP-IDE at the allosteric site of IDE and IDE residues with the thermostabilities and the flexibilities are elucidated for facilitating drug design.*

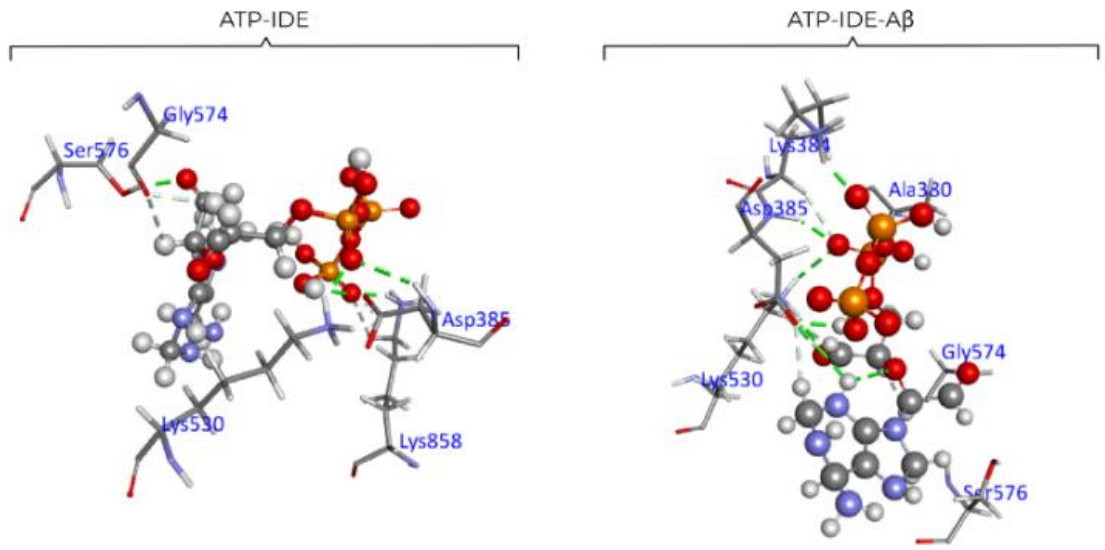

Figure 2. The hydrogen bonding interaction of the ATP-IDE and ATP-IDE-Aβ systems between ATP and the ATP-binding domain within the IDE, after QM/MM minimisation. The scaled ball is ATP (white: hydrogen, red: oxygen, gray: carbon, soft purple: nitrogen, orange: phosphorus); the dotted green line and the dotted light-green line represent the classical hydrogen bonds and the non-classical hydrogen bonds, respectively.

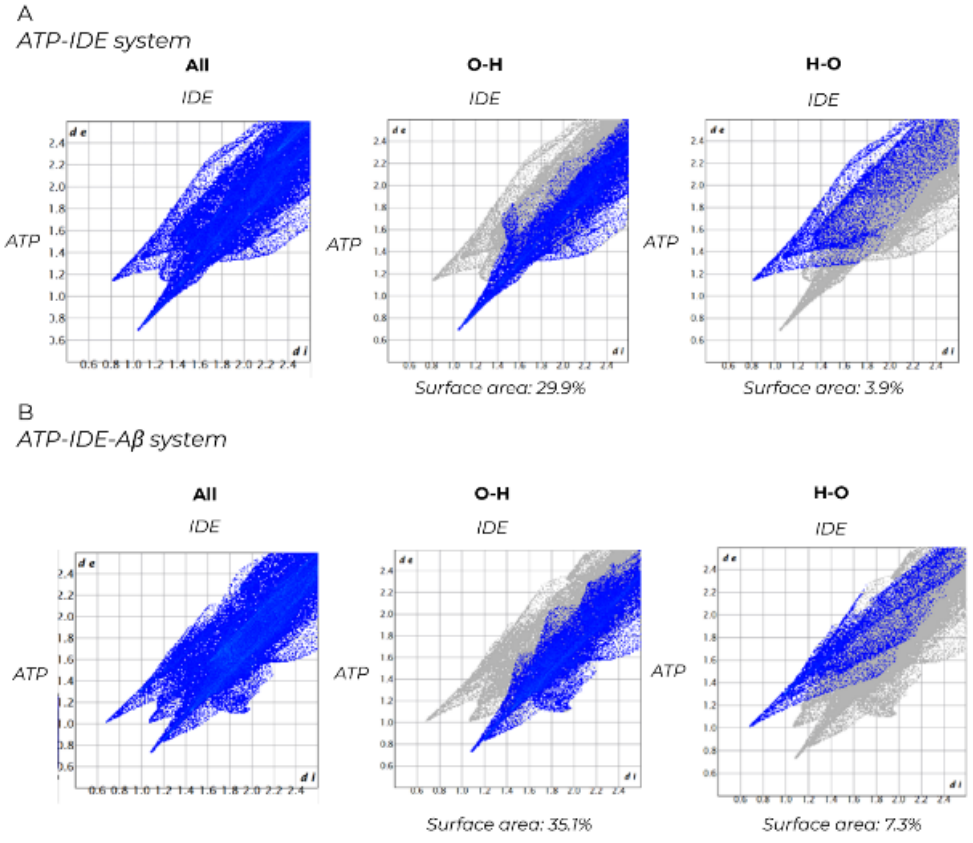

Figure 3. Surface area of hydrogen bonding interactions between ATP atoms and IDE residues through Hirshfeld surface. The hydrogen bonding interactions of Hirshfeld surface with ATP and IDE nuclei represented in dot blue. (A) Hirshfeld surface analysis of the hydrogen bonding interaction of ATP-IDE system. (B) Hirshfeld surface analysis of the hydrogen bonding interaction of ATP-IDE-Aβ system.

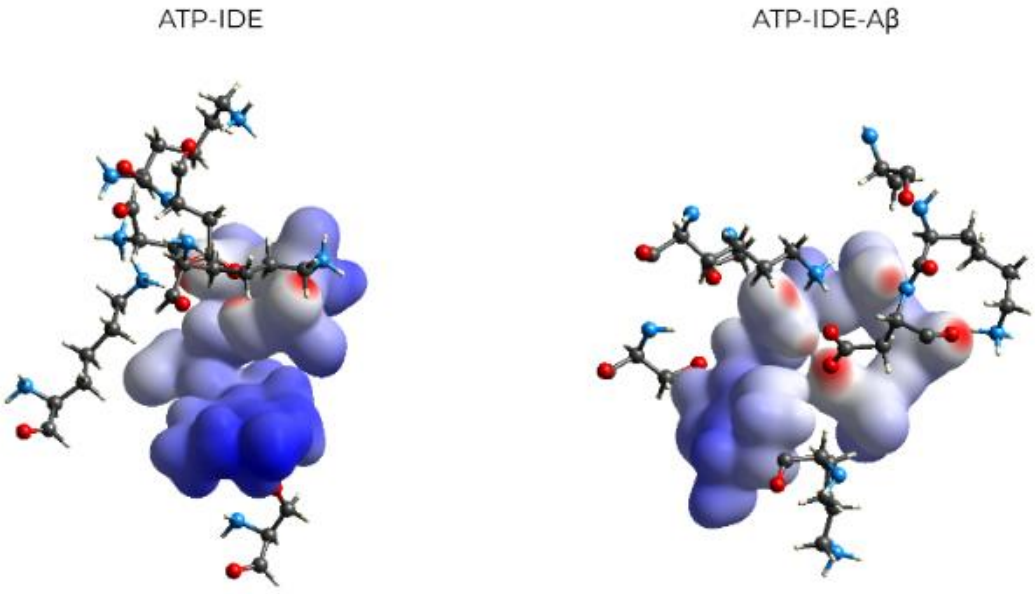

Figure 4. The Dnorm maps of ATP-IDE and ATP-IDE-Aβ systems. These Dnorm maps, based on the density functional theory (DFT) calculation, shows the electron density of ATP after QM/MM minimisation, with the ATP's proximity to the IDE residues. Both systems are shown using the same angle and settings. The red, white, and blue indicate close, medium, and little proximity, respectively.

Figure S4. The hydrogen-bond donor and acceptor sites

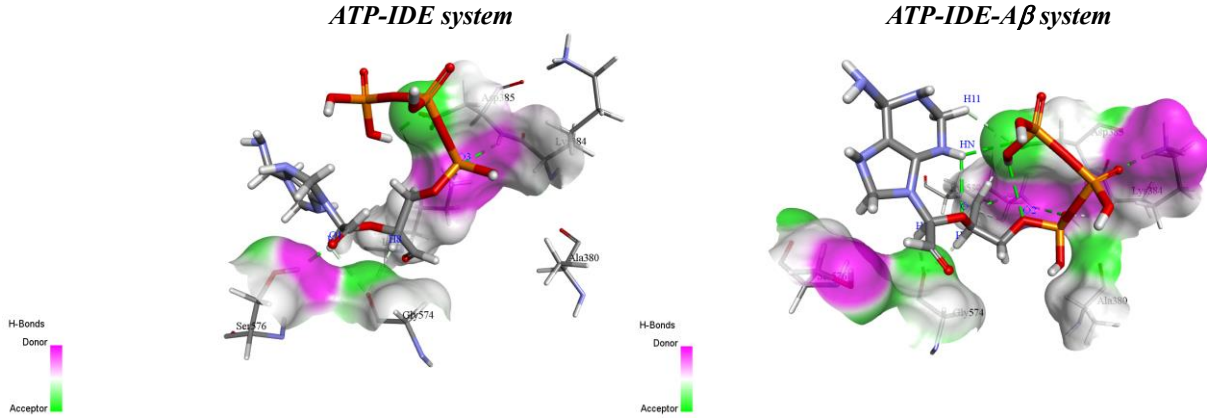

Table 3. The topological distance and energies of hydrogen bonding interactions. T: kinetic energy density (kJ/mol/Bohr^3); V: potential energy density (kJ/mol/Bohr^3); H(r): the sum of kinetic energy and potential energy; D_{cp1}, D_{cp2}: distance from the first and the second atom to the critical point, respectively; D: dissociation energy (kJ/mol); $\rho_{bcp}(r)$: electron density (eÅ^{-3}); $\nabla^2\rho(r)$: Laplacian of electron density (eÅ^{-5}).

ATP atoms	IDE residues (atoms)	V	T	|V|/T	H(r)	D_{cp1}	D_{cp2}	D	$\rho_{bcp}(r)$	$\nabla^2\rho(r)$
ATP-IDE										
H5	ASP385 (OD2)	-0.025	0.028	0.893	0.003	1.0068	0.776	113.82	0.10665	2.324
H8	GLY574 (O)	-0.008	0.1	0.080	0.092	1.0241	1.0349	30.46	0.09505	1.142

O1	SER576 (HG)	-0.029	0.03	0.967	0.001	1.1317	1.3247	50.52	0.15812	1.633
O7	LYS858 (HZ3)	-0.053	0.063	0.841	0.01	1.0722	1.2491	39.81	0.15014	1.312
O3	LYS530 (HZ3)	-0.237	0.233	1.017	-0.004	0.7198	0.4229	138.74	0.27329	3.228
O3	ASP385 (H)	-0.207	0.206	1.005	-0.001	0.6116	0.3057	131.74	0.26527	3.321
ATP-IDE-Aβ										
O3	LYS530 (HZ3)	-0.208	0.206	1.010	-0.002	0.7979	0.811	132.58	0.29856	3.132
O3	ASP385 (H)	-0.225	0.221	1.018	-0.004	0.6541	0.7261	136.91	0.27735	3.218
O12	LYS530 (HZ1)	-0.028	0.029	0.966	0.001	1.2116	1.925	99.64	0.18615	2.021
O12	LYS530 (HD3)	-0.003	0.004	0.750	0.001	1.4856	1.2441	20.68	0.04827	0.616
O3	ALA380 (HB3)	-0.004	0.006	0.667	0.002	1.4291	1.1211	21.47	0.06123	0.737
O5	LYS384 (H)	-0.043	0.057	0.754	0.014	1.0984	1.6867	86.11	0.10434	2.014
H18	ASP385 (OD2)	-0.011	0.012	0.917	0.001	2.0564	1.3152	39.77	0.1173	1.312
H5	ASP385 (CG)	-0.057	0.067	0.851	0.01	0.6483	2.0719	14.23	0.02691	0.234
H8	GLY574 (O)	-0.012	0.013	0.923	0.001	0.9247	1.7793	40.09	0.12288	1.395
H9	GLY574 (O)	-0.003	0.005	0.600	0.002	1.202	1.4849	18.41	0.05229	0.631
H15	SER576 (OG)	-0.005	0.006	0.833	0.001	1.1438	1.6151	21.88	0.06749	0.65

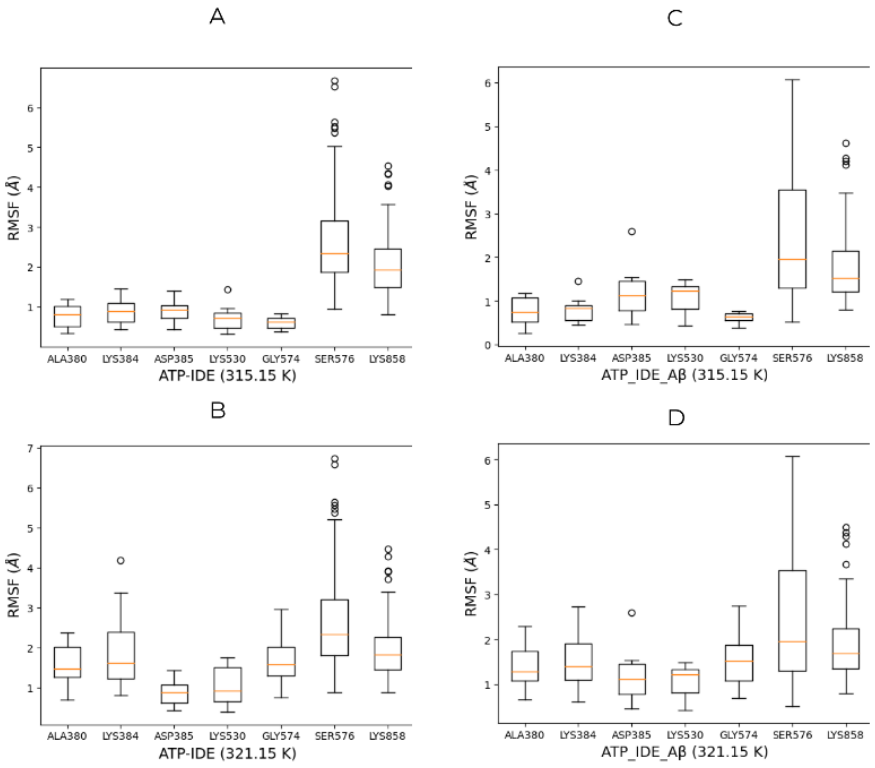

Figure 6. The root-mean-square fluctuation (RMSF) values for the IDE residues at different heat-shock temperatures. (A) The RMSF values from the ATP-IDE system after performing 2000-time steps of the MD simulation at 315.15 K and (B) at 321.15 K; (C) The RMSF values from the ATP-IDE-Aβ system after performing 2000-time steps of the MD simulation at 315.15 K and (D) at 321.15 K.