Piceatannol Binding to the Transthyretin Val122Ile Mutant: A Molecular Dynamics Investigation

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Abstract

The binding of stabilizing ligands to the protein transthyretin (TTR) were investigated with molecular dynamics simulations. TTR transports thyroid hormones in the bloodstream. The protein is a tetramer consisting of four monomers, all of which contain 127 amino acids. Mutated forms of the tetramer can dissociate into monomers that are then susceptible to aggregating into amyloid fibrils that deposit around the heart. These fibrils build up in the cardiac muscle and can cause diastolic dysfunction and lead to heart failure. The destabilizing Valine-122 to Isoleucine-122 mutation was studied here. This point mutation is common amongst older adults and about 3% of African Americans. In this study, Molecular Dynamics (MD) simulations were used to investigate the binding of the compound piceatannol (PIC) to TTR. PIC is derived from resveratrol-a natural product found in grapes and other plants. Our hypothesis was that when PIC binds to TTR it stabilizes the TTR tetramer and thus could potentially prevent its dissociation and aggregation into amyloid fibrils. The MD simulations demonstrated that piceatannol interacted with both TTR Serine-117 and Leucine-110 residues. Importantly, these interactions occurred with different TTR monomers. Therefore, the MD simulations suggest that as hypothesized the PIC ligand holds the tetramer together, by interacting with residues on different monomers. Structures of PIC bound to TTR will be presented along with studies of the mechanism of TTR stabilization by piceatannol.

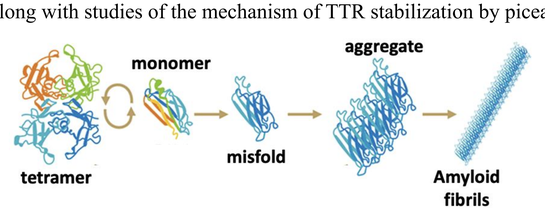
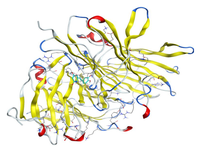


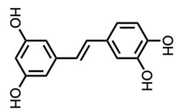
Figure 1. Destabilization of the TTR protein by the V122I mutation leading to formation of amyloid fibrils.

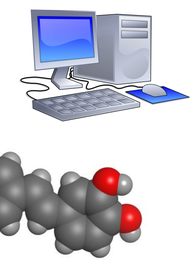
Experimental Details



Build protein-ligand complexes for the MD Simulations with ***MOE***

Run MD simulations and analyze trajectories with ***AMBER 16***.





MD Simulations Analyses Included:

1. Extracting ligand and ligand: receptor complex structures
2. Hydrogen bonds formed between ligand atoms and TTR residues
3. Solvent accessible surface areas
4. Distances between ligand atoms and TTR residues

Results

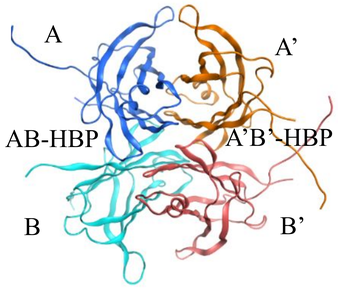


Figure 2. Structure of TTR V122I tetramer. Monomers are designated A, B, A', and B'. The halogen binding pockets (HBP) that intersect the AA' and BB' dimers are labelled AB-HBP and A'B'-HBP.

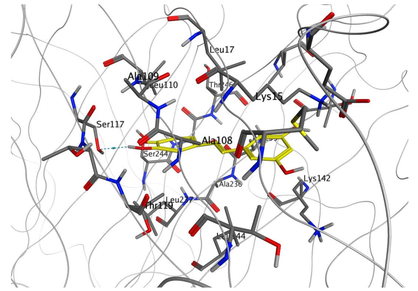


Figure 3. PIC ligand in the halogen binding pocket. The ligand and pocket residues are highlighted.

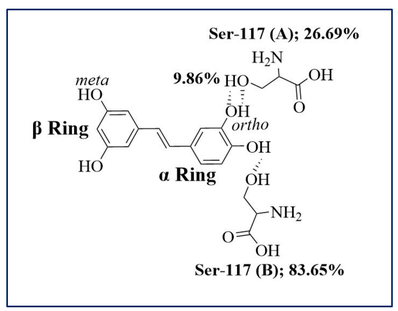


Figure 4. Analysis of hydrogen bonds formed between the PIC ligand and TTR Serine residues.

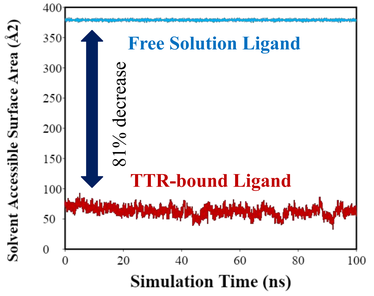


Figure 5. Ligand solvent exposure decreased upon binding to the receptor.

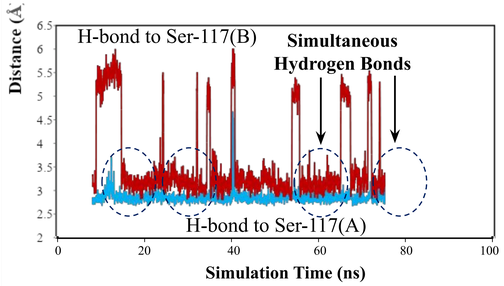


Figure 6. Distance measurements showed ligand H-bonds formed simultaneously with residues Ser-117 (A) and Ser-117 (B).

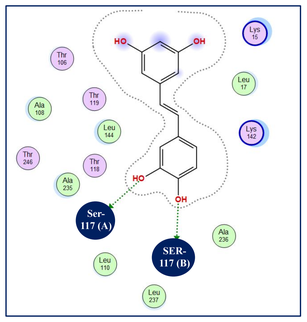


Figure 7. Residue interaction map of PIC bound to TTR at 75.3 ns. Note simultaneous H-bonds with Ser-117 (A/B) and nearby Leu-110 residues.

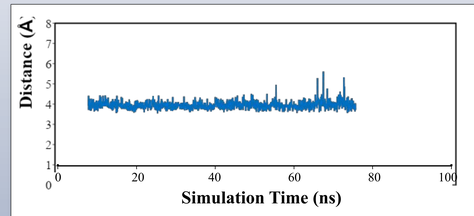
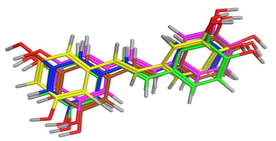


Figure 8. Distance between Leu-110 (A) δ carbons and PIC aromatic ring carbons plotted vs simulation time.



Green = 12.4 ns
Pink = 37.5 ns
Brown = 63.0 ns
Blue = 87.9 ns
Yellow = 99.7 ns

Figure 9. Ligand structures were extracted at different time steps. Superposition showed the ligand remained in the pocket throughout the MD simulation.

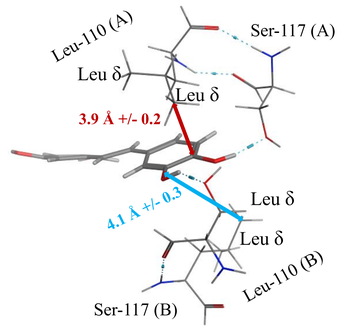


Figure 10. Shortest distances between Leu-110 (A) and Leu-110 (B) δ carbons and PIC aromatic ring. Structure was extracted at 52.3 ns.

Future Research

- Additional polyphenol ligands will be investigated, including oxyresveratrol and isorhaponbigenin
- Free energies of ligand binding to TTR will be calculated.
- Carboxylate derivatives of the ligands will be studied. Our hypothesis is that these anionic ligands will interact with cationic TTR residues like Lysine or Arginine.

References

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3. Morris, K. F., Geoghegan, R. M., Palmer, E. E., George Jr, M., & Fang, Y. (2020). Molecular dynamics simulation study of AG10 and tafamidis binding to the Val122Ile transthyretin variant. *Biochemistry and Biophysics Reports*, 21, 100721.

Acknowledgements

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