

Supplementary Information

The Norepinephrine Transporter- $G\beta\gamma$ Subunit Interaction Promotes Norepinephrine Efflux through the Transporter: *In silico* and Functional Studies

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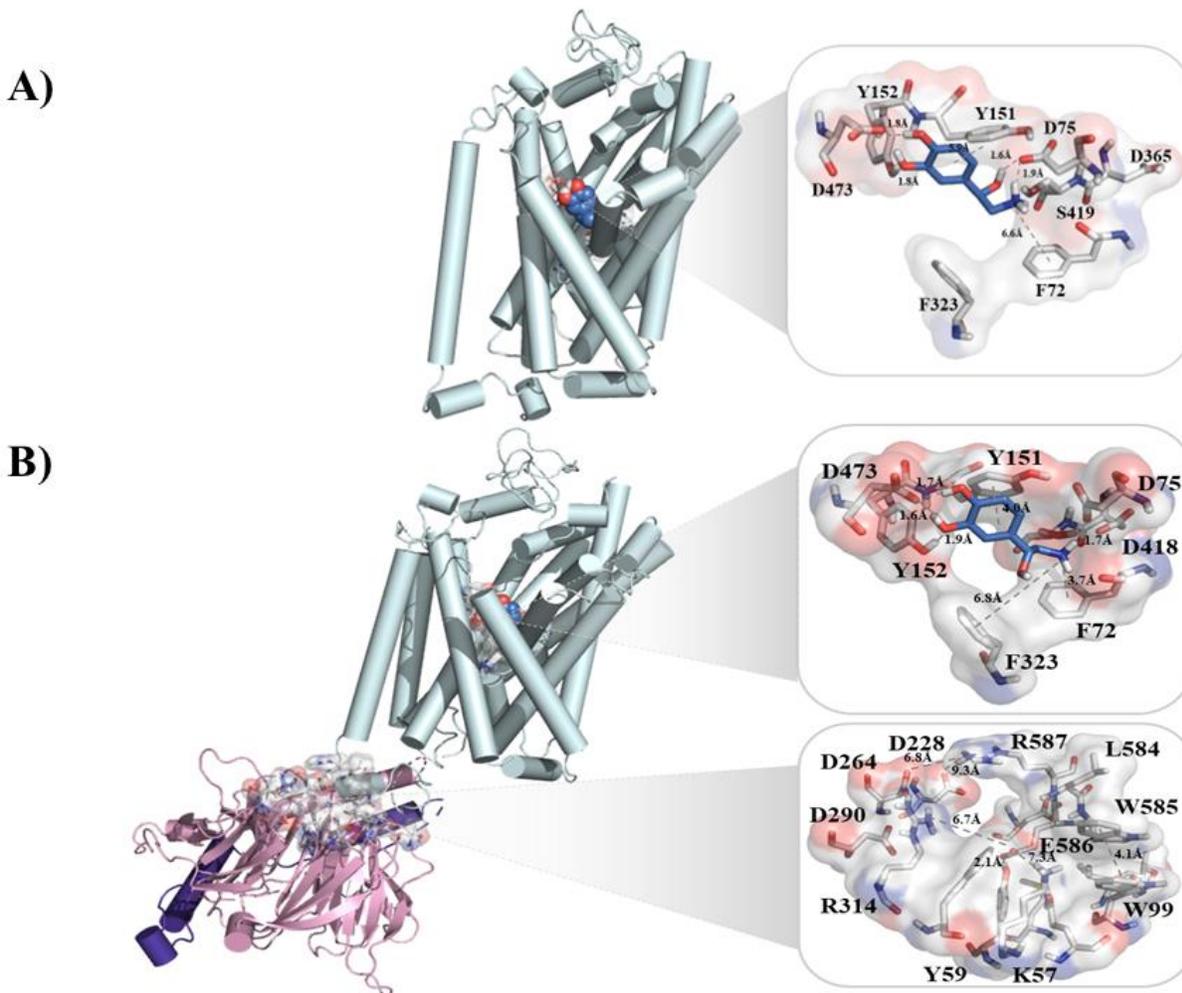


Figure S1: Docking of NET with NE using Autodock4 and NET/Gβγ using HADDOCK2.4. A) Tridimensional representation of the NET/NE complex and the main interactions at the binding site. B) Tridimensional representation of the NET/NE/Gβγ complex and the primary interaction with NE at the binding site and the NET/Gβγ contact interface.

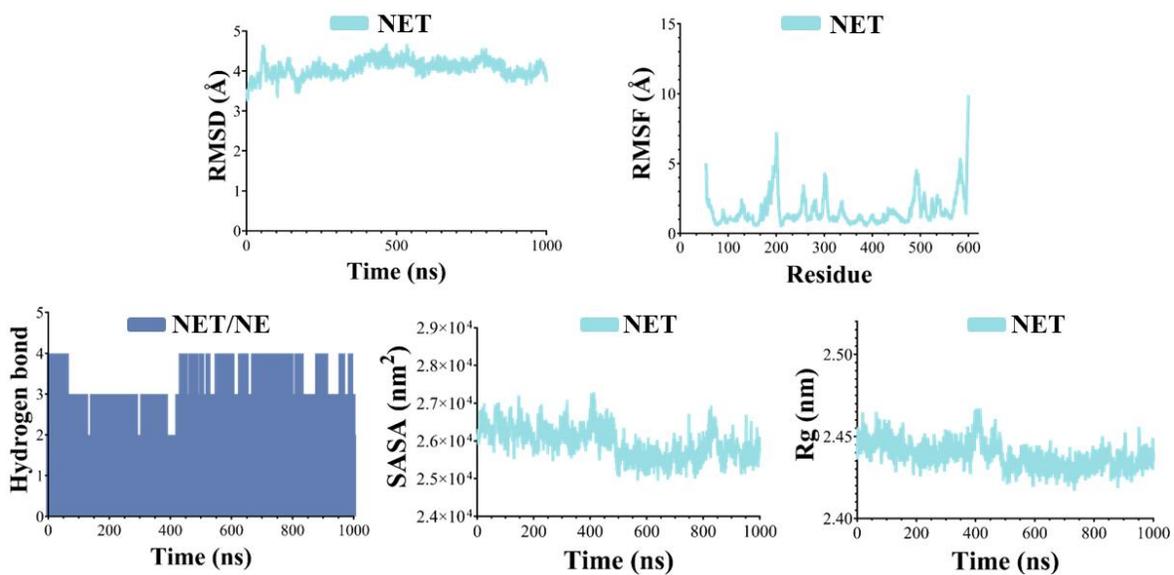


Figure S2: Analysis of NET/NE complex from molecular dynamic simulation. The RMSD, RMSF, SASA, and Radius of gyration (Rg) during 1.5 μ s of simulation are shown.

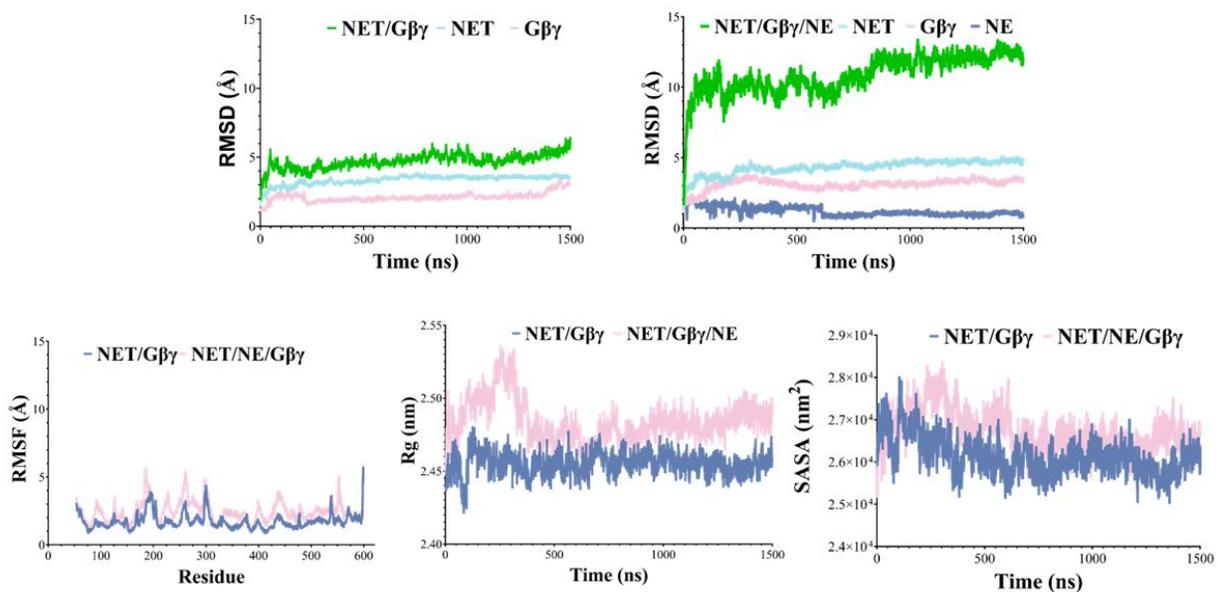


Figure S3: Analysis of NET/NE/G $\beta\gamma$ system from molecular dynamic simulation. The RMSD, RMSF, SASA, and Radius of gyration during 1.5 μ s of simulation.

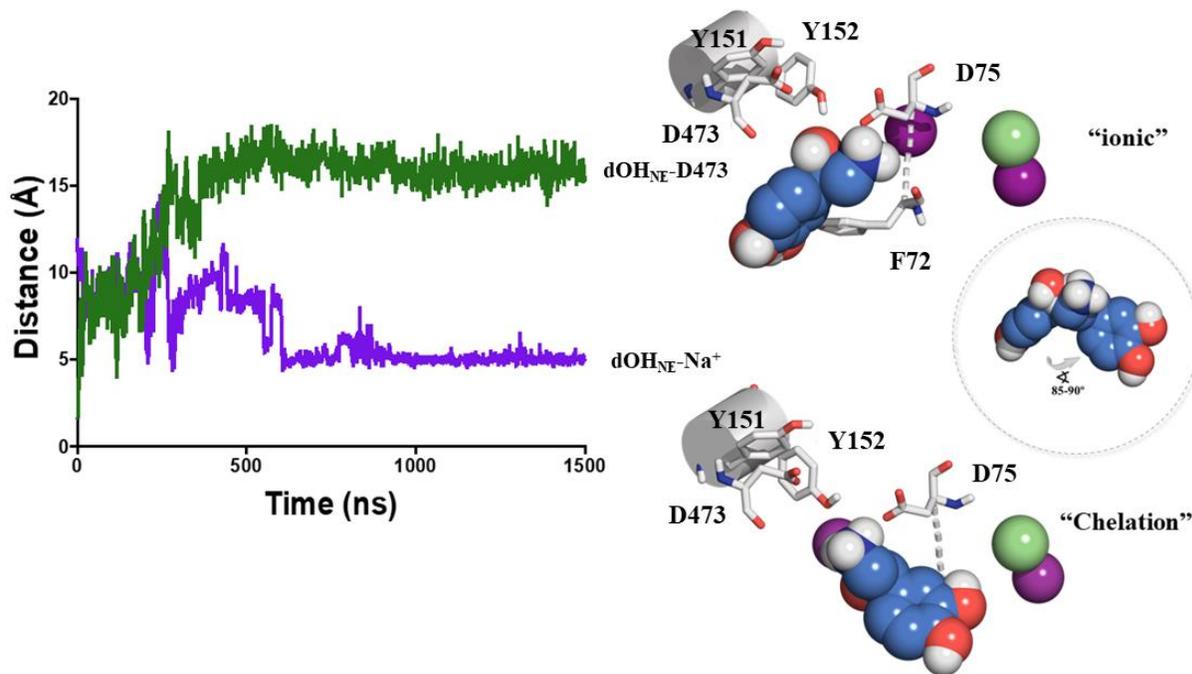


Figure S4: Distance of hydroxyl group of NE to D420 and sodium ion respectively during the simulation. The ionic and chelation modes of NE interacting in NET is displayed. The circle inset shows the change in the angle of NE into the NET cavity.

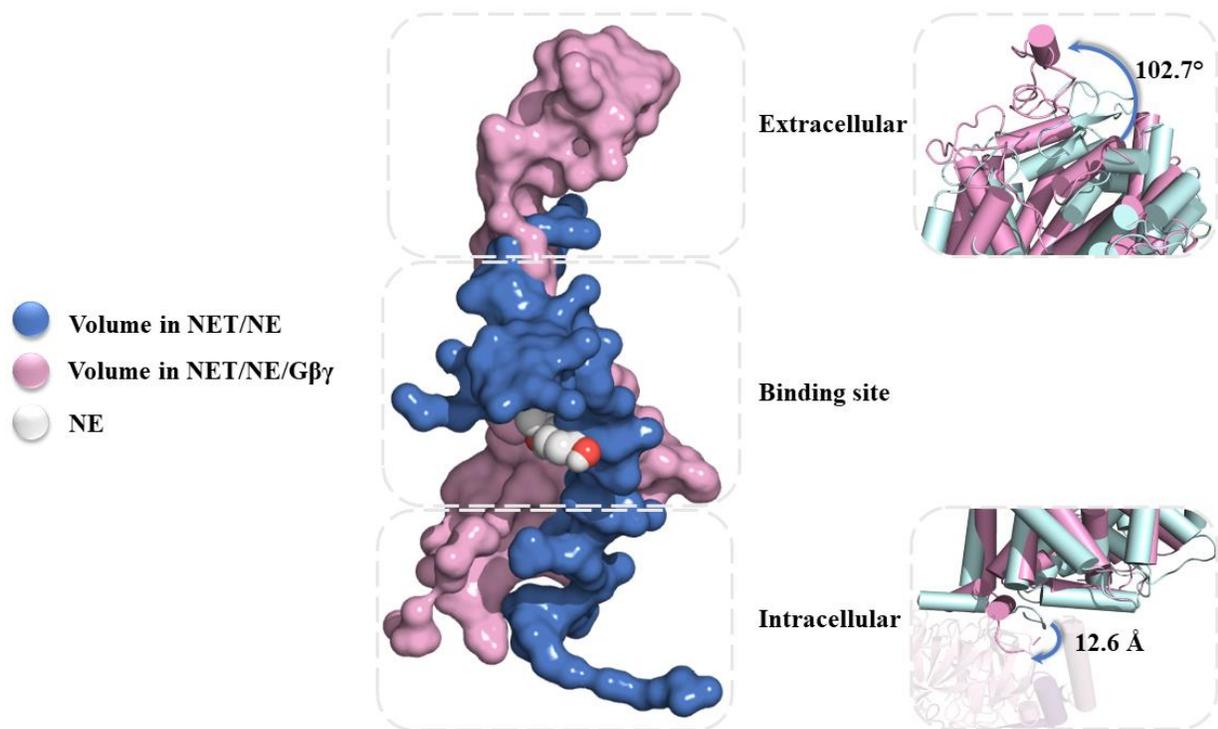


Figure S5: Superposition of the volumes detected using Hollow in NET/NE and NET/NE/Gβγ complex after 1.5 μs of simulation. The image shows the opening at the extracellular level of NET when Gβγ and NE are present.