Arginine-Vasopressin and its V2 Receptor: Binding Pathways, Kinetics and Thermodynamics

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G-protein coupled receptors, GPCRs, are a family of highly similar membrane proteins that plays a critical role in cell communication. However, the crystallization of GPCRs remains far more challenging than for soluble proteins. Despite the absence of crystal structures for the vasopressin receptor subtypes, mutagenesis studies aimed at characterizing the receptor-ligand binding and essential interacting domains have shed some light on interactions between the receptor and the peptide hormone. Arginine vasopressin (AVP) is a neuropeptide most well known for its antidiuretic and vasopressor effects. The vasopressin 2 receptor (V2R) is of particular interest because it is localized in the renal collecting duct and represents a selective target for the antidiuretic effect of AVP.

We used a neurotensin carrier protein complex (PDB ID: 4GRV)[1] as a template after reconstruction of a missing N-terminusm that has been described to be essential for AVP binding [2]. Long-scale molecular dynamics (MD) simulations were used to determine the structure of the V2R-AVP complex and, in conjunction with enhanced sampling techniques to simulate the docking event and estimate the binding free energy. Possible binding pathways were thus identified and potential allosteric binding site for the design of V2R antagonists detected.

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[2] Hawtin, S. R.; Wesley, V. J.; Parslow, R. A.; Patel, S.; Wheatley, M. Biochemistry 2000, 39, 13524.