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10 Interactions of a Glucagon-like peptide 1 and a Glucagon-like peptide 1 analogue, liraglutide, with the endogenous receptor

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We have investigated the interactions of the Glucagon-like peptide 1 (GLP-1) and a GLP1 analogue, liraglutide, with the endogenous receptor using molecular dynamics (MD) simulations. It is evident that the attached fatty acid (FA) chain in liraglutide enhances the affinity for the GLP-1 receptor since liraglutide binds approximately 10 times stronger to the receptor than GLP-1 [1,2]. Our hypothesis is that the FA chain will interact with the hydrophobic pocket of the extracellular domain (ECD) and thus strengthen the interactions between the peptide and the receptor compared to GLP-1. Furthermore, the shape of the ligand is of importance to the affinity as more interactions can be obtained if the ligand is shaped so that its N-terminal can interact with the top of the transmembrane (TM) region. To shed light on these differences, simulations were performed on fully hydrated receptor-ligand complexes in a 1-palmitoyl-2-oleoylphosphatidylcholine membrane. The receptor structure was built from the experimentally determined ECD structure (PDB entry 3IOL; [3]) and a homology model structure of the 7 alpha helix TM region using the class B human glucagon G protein coupled receptor structure (4L6R; [4]). To address the importance on the shape of the peptide, both the GLP-1 and the liraglutide complexes are built in two conformations; one where the ligands are simulated in the L-shape as seen in the crystal structure 1JRJ and described by Thornton and Gorenstein [5], and one where they are in a straight form as seen in the crystal structures 4APD and 3IOL. Preliminary results show that the complex maintains its overall structure. Slight rearrangements are observed in the TM region, where it turns slightly around its own axis to adjust to the surrounding phospholipids. The same applies for the secondary structure in ECD, which is preserved throughout the simulations. A displacement is observed where ECD moves away from the TM region which results in an extension of the GLP-1 N-terminal and the coil region around the middle kink. This movement occurs on a relatively short time scale, and it happens within the first 20 ns. This is most likely in response to the adaption of the TM region to the lipid environment. The stability is, however, maintained since the overall secondary structure of both ECD and the peptide is preserved through this extension. Although an extension of the peptide occurs, the interactions reported between GLP-1 and ECD are withheld throughout the simulations. Further analyses are in progress and should be able to identify the key interactions that determine the difference in binding affinity of GLP-1 and liraglutide towards the endogenous receptor.

[1] Thorkildsen, C. et al., 2003, JPET 307:490-496. [2] Secher, A. et al., 2014, J. Clin. Invest. 124(10):4473-4488. [3] Underwood, C. R. et al., 2010, J. Biol. Chem., 285:723-730. [4] Siu, F. Y. et al., 2013, Nature 499:444-449. [5] Thornton, K. & Gorenstein, D.G. Biochemistry 1994, 33:3532-3539.

11 Discovery of CREBBP bromodomain ligands by high-throughput docking and hit optimization guided by molecular dynamics

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We have identified two chemotypes of CREBBP bromodomain ligands by fragment-based high-throughput docking with a hit rate of 12%. Guided by the docked pose and molecular dynamics simulations, one of the two hits was improved by medicinal chemistry into a low nanomolar lead with very good ligand efficiency and selectivity as measured by isothermal titration calorimetry. The crystal structures of a nanomolar derivative has validated the pose of the hit obtained in silico. Some of the derivatives inhibit proliferation of a small subset of leukemia cell lines.