Histamine H_2 Receptor in complex with G_s protein: a comprehensive molecular dynamics study

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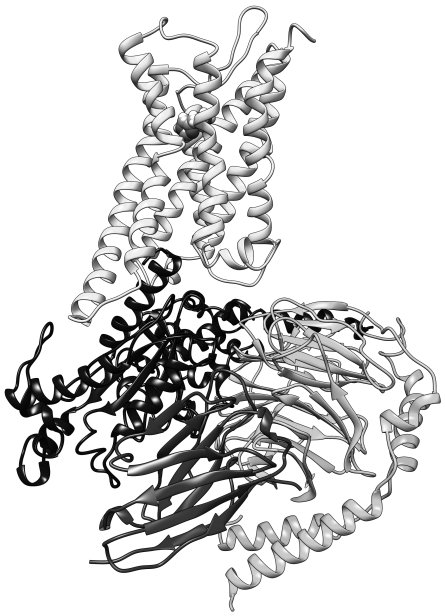

The histamine H_2 receptor plays an important role in the regulation of gastric acid secretion. Therefore, it is a main drug target for the treatment of gastroesophageal reflux or peptic ulcer disease [1]. However, to date there is no crystal structure available for this receptor, which would be a prerequisite for *rational* drug design. Hence we created a model of the active histamine H_2 receptor-G_s complex based on the structure of the ternary complex of the β_2 adrenoceptor [2]. The binding mode of its natural ligand histamine was deduced using a multiple walker metadynamics protocol [3],[4]. We conducted further refinements by conventional molecular dynamics simulations and used the resulting structure to examine the interactions of the receptor with histamine and the G_s protein. To further validate the model and investigate its switchability towards the inactive ensemble we conducted several simulations including gaussian accelerated molecular dynamics [5] in which the G protein was removed. Since the main G protein interaction is mediated by the $\alpha 5$ helix of G_s, we additionally simulated a shortened version of the G_s, namely the terminal $\alpha 5$ helix to examine whether this part is sufficient to maintain the active conformation. The overall results of our study provide detailed insights into the dynamics of the H_2 receptor complex that can contribute to future drug development.

[1] Stephen Holt. "Over-the-Counter Histamine H 2-Receptor Antagonists". In: *Drugs* 47.1 (1994), pp. 1–11.

[2] Søren GF Rasmussen et al. "Crystal structure of the β-2-adrenergic receptor–Gs protein complex". In: *Nature* 477.7366 (2011), p. 549.

[3] Noureldin Saleh et al. "An efficient metadynamics-based protocol to model the binding affinity and the transition state ensemble of G-protein-coupled receptor ligands". In: *Journal of chemical information and modeling* 57.5 (2017), pp. 1210–1217.

[4] Christian A Söldner, Anselm HC Horn, and Heinrich Sticht. "Binding of histamine to the H1 receptor—A molecular dynamics study". In: *Journal of molecular modeling* 24.12 (2018), p. 346.

[5] Yinglong Miao, Victoria A Feher, and J Andrew McCammon. "Gaussian accelerated molecular dynamics: Unconstrained enhanced sampling and free energy calculation". In: *Journal of chemical theory and computation* 11.8 (2015), pp. 3584–3595.