Binding of histamine to the H_1 receptor: a molecular dynamics study

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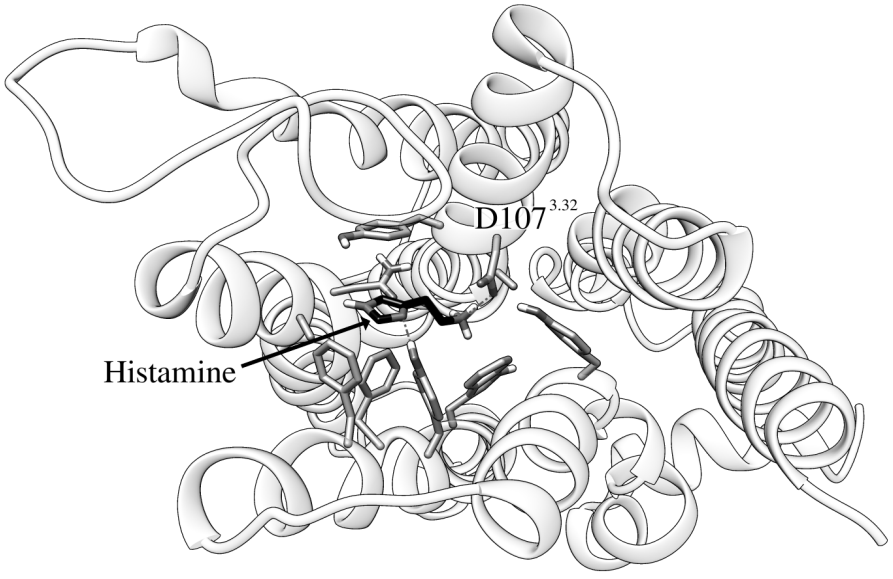
Binding of histamine to the G-protein coupled histamine H_1 receptor plays an important role in the context of allergic reactions [1]; however, no crystal structure of the resulting complex is available yet. To deduce the histamine binding site, we performed unbiased molecular dynamics (MD) simulations on a microsecond time scale, which allowed to monitor one binding event, in which particularly the residues of the extracellular loop 2 were involved in the initial recognition process.

The final histamine binding pose in the orthosteric pocket is characterised by interactions with Asp107$^{3.32}$, Tyr108$^{3.33}$, Thr194$^{5.43}$, Asn198$^{5.46}$, Trp428$^{6.48}$, Tyr431$^{6.51}$, Phe432$^{6.52}$, and Phe435$^{6.55}$, which is in agreement with existing mutational data [2–4]. The conformational stability of the obtained complex structure was subsequently confirmed in 2 μs equilibrium MD simulations, and a metadynamics simulation proved that the detected binding site represents an energy minimum.

A complementary investigation of a D107A mutant, which has experimentally been shown to abolish ligand binding [2], revealed that this exchange results in a significantly weaker interaction and enhanced ligand dynamics. This finding underlines the importance of the electrostatic interaction between the histamine ammonium group and the side chain of Asp107$^{3.32}$ for histamine binding.



Final binding mode of histamine to the H_1 receptor. Histamine and the most important interacting residues of the receptor are shown as sticks. For clarity, the histamine carbon atoms are coloured in black.

References

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