Mechanics of Histamine: Computational analysis of protonation effects on H_1R binding.

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Based on a structure of the ternary histamine-H_1R-Gq complex, we investigated the role of different protonation states of histamine for binding the H_1-receptor. Molecular dynamics simulations revealed that the τ-tautomer of histamine formed stable interactions with the receptor. A π-tautomer, on the other hand, induces a rotation of the histamine ring by 180°. The simulations thus indicate that the τ-tautomer of histamine is the relevant protonation state that stabilizes the active ternary histamine-H_1R-G_q complex. In addition to the tautomers, the binding of a dicationic histamine was investigated, whose interaction with the H_1R was shown in a previous experimental study. The simulations demonstrated that the dication is less compatible with the ternary histamine-H_1R-G_q complex than the monocation and in one case even dissociates. The studies performed in this work thus provided contributions to the mechanistic understanding of histamine receptors, which may be used for future design approaches in drug development.