

# Ligand-Specific Contribution of the N-Terminus and E2-Loop to Pharmacological Properties of the Histamine H<sub>1</sub>-Receptor

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## Abstract

There are species-differences between human histamine H<sub>1</sub> receptor (hH<sub>1</sub>R) and guinea pig histamine H<sub>1</sub> receptor (gpH<sub>1</sub>R) for phenylhistamines and histaprodifens. Several studies showed participation of the second extracellular loop (E2-loop) in ligand-binding for some G-protein-coupled receptors (GPCRs). Because there are large species-differences in amino acid sequence between hH<sub>1</sub>R and gpH<sub>1</sub>R for the N-terminus and E2-loop, we generated chimeric hH<sub>1</sub>Rs with gp-E2-loop (h<sub>gpE2</sub>H<sub>1</sub>R) and gp-N-terminus and gp-E2-loop (h<sub>gpNgpE2</sub>H<sub>1</sub>R). hH<sub>1</sub>R, gpH<sub>1</sub>R and chimeras were expressed in Sf9 insect cells. [<sup>3</sup>H]Mepyramine binding assays and steady-state GTPase assays were performed. In the series hH<sub>1</sub>R > h<sub>gpE2</sub>H<sub>1</sub>R > h<sub>gpNgpE2</sub>H<sub>1</sub>R we observed a significant decrease in potency of histamine **1** in the GTPase assay. For phenoprodifen **5** and the chiral phenoprodifens **6R** and **6S** a significant decrease in affinity and potency was found in the series hH<sub>1</sub>R > h<sub>gpE2</sub>H<sub>1</sub>R > h<sub>gpNgpE2</sub>H<sub>1</sub>R. Additionally, we constructed new active-state H<sub>1</sub>R models based on the crystal structure of the human β<sub>2</sub>-adrenergic receptor. Compared to the H<sub>1</sub>R active-state models based on the crystal structure of bovine rhodopsin, the E2-loop differs in its contact to the ligand bound in the binding pocket. In the bovine rhodopsin based model, the backbone carbonyl of Lys-187 (gpH<sub>1</sub>R) interacts with large histaprodifens in the binding pocket, but in the hβ<sub>2</sub>AR based model Lys-187 (gpH<sub>1</sub>R) is located distantly from the binding pocket. In conclusion, the differences in N-terminus and E2-loop between hH<sub>1</sub>R and gpH<sub>1</sub>R exert an influence on affinity and/or potency for histamine and phenoprodifens **5**, **6R** and **6S**.