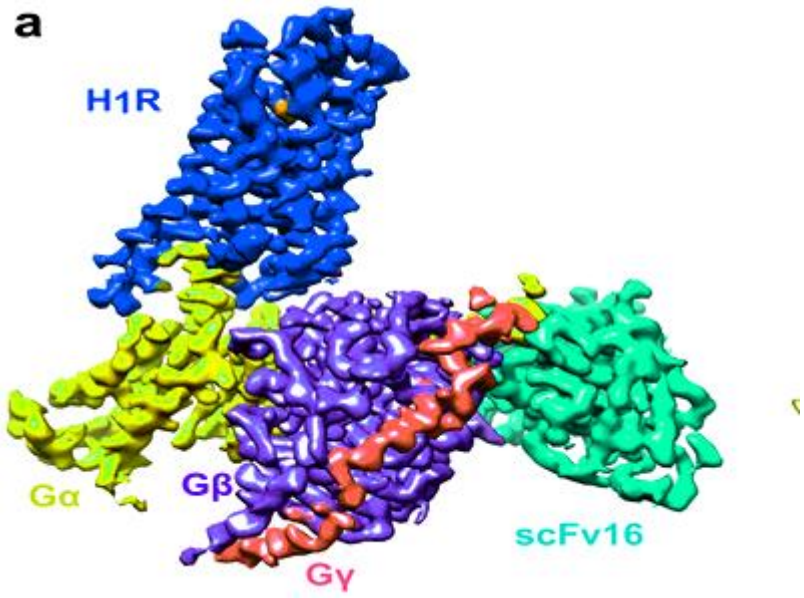
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, positive-sense, single-stranded RNA virus, which enters host cells through two major routes. Following the recognition and binding of the SARS-CoV-2 spike (S) protein to the angiotensin-converting enzyme 2 receptor (ACE2), the S protein is primed and activated by cellular proteases such as transmembrane serine protease 2 (TMPRSS2), followed by the fusion of viral and plasma membranes and subsequent release of viral genomic RNA. In cells lacking sufficient TMPRSS2, SARS-CoV-2 enters host cells *via* the endocytic pathway. The research group from China performed this *in vitro* and animal study to investigate whether histamine receptor H1 (HRH1) acts as an independent receptor for SARS-CoV-2. These authors and others have previously discovered that antihistamine drugs, particularly HRH1 antagonists, potently inhibit SARS-CoV-2 infection.

The SARS-CoV-2 genome encodes four structural proteins, namely the spike (S), envelope (E), nucleocapsid (N), and membrane (M) protein. The S protein is a glycosylated homotrimer with each monomer composed of subunits S1 and S2. The S1 domain comprises the N-terminal domain (NTD), the receptor binding domain (RBD) with a receptor binding motif (RBM), and two C-terminal domains. The RBD in the S1 subunit recognizes human ACE2 and is responsible for attachment to host cells.

Multiple reports have revealed that SARS-CoV-2 can utilize accessory or alternative receptors to facilitate hACE2-dependent or hACE2-independent entry. Neuropilin-1 receptor binds directly to the furin-cleaved S1 subunit and serves as the secondary cofactor for hACE2-dependent viral entry. Other coreceptors, like lysosomal transmembrane protein TMEM106B, have been found to facilitate hACE2-independent viral entry. The affinity of the interaction between the S protein and TMEM106B was lower than that of the S protein binding to ACE2, but it was similar to the affinity of the S protein binding to neuropilin 1. https://discovermednews.com/tmem106b-protein-is-an-independent-receptor-for-sars-cov-2-entry-into-ace2-negative-host-cells/

The authors emphasized that several antihistamine drugs, including clemastine, astemizole, azelastine, brompheniramine, and ebastine, used for treating allergy symptoms, have been found to prevent SARS-CoV-2 infection or replication. Notably, all of these antihistamines are HRH1 antagonists, suggesting an important role for HRH1 in the SARS-CoV-2 infection.



About the study

The authors proposed a model for HRH1-mediated SARS-CoV-2 entry. In cells susceptible to SARS-CoV-2, which express high levels of ACE2 and low levels of HRH1 (ACE2 high/HRH1 low cells), the viral S proteins directly bound to the cellular ACE2 receptors, thereby facilitating the subsequent fusion of viral and cellular membranes and release of viral genomic RNAs. However, in cells that express insufficient ACE2 but high levels of HRH1 (ACE2 low/HRH1 high cells), SARS-CoV-2 alternatively uses HRH1 as a receptor to bind to SARS-CoV-2 S proteins.

HRH1 acts as an hACE2-independent receptor for SARS-CoV-2 by binding directly to the NTD of the S proteins.

Interestingly, in susceptible cells that expressed medium levels of both, ACE2 and HRH1 (ACE2 medium/HRH1 medium cells), SARS-CoV-2 entered the cytoplasm in an ACE2/HRH1-dependent manner. HRH1 enhanced ACE2-dependent viral entry in major SARS-CoV-2 variants, suggesting an important synergistic effect of HRH1 and hACE2, which led to facilitated SARS-CoV-2 entry.

Authentic virus infection assays and transgenic hACE2 mouse challenge experiments further confirmed that antihistamine drugs effectively inhibited the binding of HRH1 to the S

protein and viral infection. Six antihistamine drugs of the first generation, namely, brompheniramine, clemastine, cyproheptadine, diphenhydramine, promethazine, and triprolidine, as well as five antihistamine drugs of the second generation, namely, acrivastine, astemizole, azelastine, desloratadine, and loratadine inhibited SARS-CoV-2 infection, with half maximal inhibitory concentrations (IC50) ranging from 1.625 to 4.816 µM. The prophylactic effects of these drugs were further confirmed in transgenic hACE2 mice challenged with SARS-CoV-2, in which acrivastine treatment inhibited SARS-CoV-2 infection.

Conclusion

This study revealed that histamine receptor H1 acts as an independent receptor for SARS-CoV-2, binding directly to the NTD of the S protein. Additionally, HRH1 directly interacted with ACE2 and synergistically enhanced ACE2-dependent viral entry. The antihistamine drugs effectively inhibited the binding of HRH1 to the S protein and viral infection.

The authors concluded that they provided compelling evidence that HRH1 acts as an alternative receptor for SARS-CoV-2 and that the administration of antihistamine drugs could be used as a potential treatment for COVID-19.

This article was published in mBIO (ASM Journals).

Journal Reference

Yu F, et al. The histamine receptor H1 acts as an alternative receptor for SARS-CoV-2. (Open Access) mBio0:e01088-24. https://journals.asm.org/doi/10.1128/mbio.01088-24.