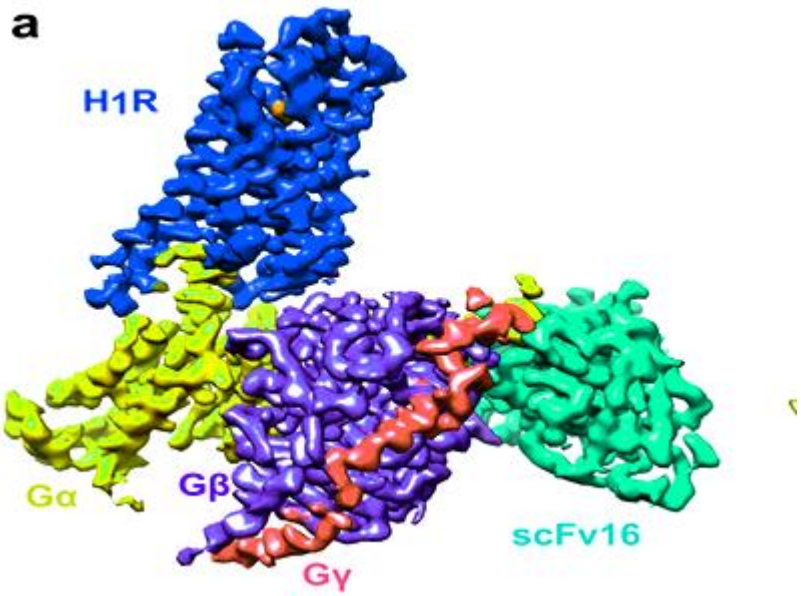
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, positive-sense, single-stranded RNA virus that enters host cells through two major routes. After the recognition and binding of the SARS-CoV-2 spike (S) protein to the angiotensin-converting enzyme 2 receptor (ACE2), the S protein is primed and activated by cellular proteases such as transmembrane serine protease 2 (TMPRSS2). This is followed by the fusion of viral and plasma membranes and the subsequent release of viral genomic RNA. In host cells lacking sufficient TMPRSS2, SARS-CoV-2 enters through the endocytic pathway. Since numerous studies have reported that SARS-CoV-2 utilizes accessory or alternative receptors to facilitate hACE2-dependent or hACE2-independent entry, the Chinese research group performed this *in vitro* and animal study to investigate whether the histamine receptor H1 (H1R) acts as an independent receptor for SARS-CoV-2.

The authors of this study and other researchers have previously observed that antihistamine drugs, particularly H1 antagonists, potently inhibit SARS-CoV-2 infection. 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 H1R antagonists, suggesting an important role for H1R in SARS-CoV-2 infection.



The SARS-CoV-2 spike (S) protein, which appears to be a major pathogenic factor contributing to the unique pathogenesis of SARS-CoV-2, is a glycosylated homotrimer, with

each monomer composed of subunits S1 and S2. The S1 subunit comprises the N-terminal domain (NTD), the receptor binding domain (RBD) with a receptor binding motif (RBM), and two C-terminal domains.

About the Study and Results

In cells expressing high levels of ACE2 and low levels of H1R (ACE2 high/H1R low), the SARS-CoV-2 S protein was directly bound to the cellular ACE2 receptors. However, in cells expressing insufficient levels of ACE2 but high levels of H1R (ACE2 low/H1R high), SARS-CoV-2 S protein alternatively used H1R as an hACE2-independent receptor. In cells expressing medium levels of both ACE2 and H1R (ACE2 medium/H1R medium), H1R facilitated ACE2-dependent viral entry, suggesting an important synergistic effect of H1R and hACE2.

H1R was bound directly to the NTD on the S1 subunit.

A SARS-CoV-2 infection assay further confirmed that antihistamines effectively inhibited the binding of H1R 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.

Furthermore, acrivastine treatment of transgenic hACE2 mice challenged with SARS-CoV-2, inhibited SARS-CoV-2 infection and confirmed the prophylactic effects of these drugs.

Conclusion

This study revealed that histamine receptor H1 binds directly to the NTD on the S1 subunit and acts as an hACE2-independent receptor for SARS-CoV-2. It also synergistically interacts with ACE2 and facilitates ACE2-dependent viral entry.

A SARS-CoV-2 infection assay and animal study further confirmed that antihistamine drugs effectively inhibit the binding of H1R to the S protein and viral infection. The authors concluded that these results suggest that antihistamine administration could be a potential treatment for COVID-19.

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