

# Histamine H1 Receptor Antagonists

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Histamine H1 receptor (H1 receptor) antagonists are widely prescribed medications to treat allergic diseases, while recently it has emerged that they show significant promise as anti-SARS-CoV-2 agents.

COVID-19

NF-κB signaling

H1 receptor antagonists

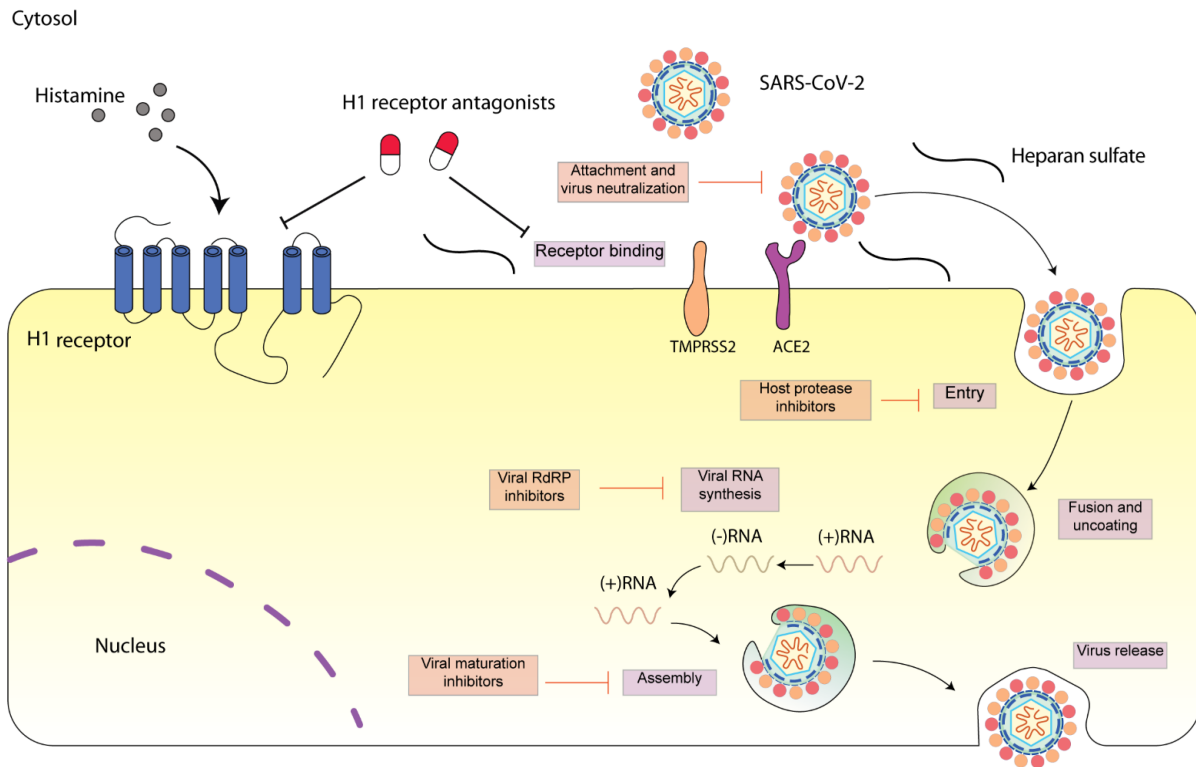
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## 1. Introduction

Coronavirus disease 2019 (COVID-19), an emerging respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is swiftly leading to global health issues and becoming a pandemic worldwide. It forces much of the world to adopt a lockdown mode, causing enormous economic fallout and human suffering. Most patients with COVID-19 are either asymptomatic or show mild symptoms; however in some cases, patients progress to severe lung injuries and eventually develop multiple organ failure [\[1\]\[2\]](#).

SARS-CoV-2 is a single-stranded, positive-sense RNA virus (++ssRNA) [\[3\]](#). The SARS-CoV-2 genome possesses an 82% sequence identity to that of SARS-CoV and MERS-CoV. Four structural proteins including spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins have been identified in SARS-CoV-2. These protein sequences are also highly similar to that of SARS-CoV and MERS-CoV [\[4\]](#). The viral structural proteins play vital roles in determining the viral life cycle, and thus provide potential therapeutic targets [\[5\]](#). SARS-CoV-2 engages SARS-CoV angiotensin converting enzyme 2 (ACE2) receptor for entry and transmembrane serine protease (TMPRSS2) for S protein priming. After entering the cell, SARS-CoV-2 is subsequently taken up into endosomes and then fused with lysosomal membranes. Eventually, SARS-CoV-2 virions are released from the cell through exocytosis (Figure 1) [\[6\]](#). SARS-CoV-2 infection can cause severe respiratory pathologies and lung injuries [\[7\]](#). The severity of the lung injuries is correlated with the production of a cytokine storm by the macrophages during SARS-CoV-2 infection. High levels of cytokines including IL-2, IL-10, GCSF, IP-10, MCP-1, IL-7, TNF- $\alpha$ , and MIP-1A were observed in COVID-19 patients at high risk of mortality [\[1\]](#). In parallel, an enhanced concentration of perivascular and septal mast cells was found in post-mortem lung biopsies of COVID-19 [\[8\]](#). Mast cells synthesize and secrete inflammatory mediators including histamine. The roles of mast cells in SARS-CoV-2 infection have been frequently discussed [\[9\]\[10\]\[11\]\[12\]](#). Whether histamine released by mast cell activation during SARS-CoV-2 infection contributes to the severity of lung injury remains to be elucidated [\[13\]\[14\]](#).



Schematic diagram presenting life cycle of SARS-CoV-2 and relevant inhibitors. SARS-CoV-2 cell entry begins with binding of the spike S protein to ACE2, a process that is facilitated by TMPRSS2. SARS-CoV-2 enters the cell through endocytosis, and then the virus is uncoated in the acidic environment of lysosomes. After that, SARS-CoV-2 RNA is released, followed by the reproduction of virus genome and viral proteins. Then, the viral components are assembled and released via exocytosis [15]. Each step can be targeted by relevant inhibitors. H1 receptor antagonists may inhibit SARS-CoV-2 either via H1 receptor or via ACE2 receptor. SARS-CoV-2 spike protein interacts with both cellular heparan sulfate and ACE2 through its receptor-binding domain (RBD) [16]. H1 receptor antagonists may disrupt the interaction between heparan sulfate and spike protein, inhibiting SARS-CoV-2 entry.

In most cases, the excess lung inflammation response caused by SARS-CoV-2 is self-competent; however, in some patients, it is unbalanced and non-competent, with age and comorbidities such as arterial hypertension or diabetes being acknowledged as risk factors. As a consequence, these patients require hospitalization and need to be managed appropriately. Considering the alleviation of the inflammatory response and concomitant lung injuries, anti-inflammatory drugs (non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids) are being administered to COVID-19 patients with various treatment regimens [17][18]. However, debates exist regarding their clinical use in COVID-19 patients [19][20]. For instance, ibuprofen, an over-the-counter medication used for the treatment of pain and fever in COVID-19, has been found to increase ACE2 levels [21]. In terms of corticosteroids, a recent study showed that low-dose dexamethasone, particularly in critically ill COVID-19 patients (i.e., ICU-hospitalized patients with respiratory distress), significantly improved patient survival [22]. Nevertheless, it may disrupt the immunocompetence in COVID-19 patients [23][24][25].

Histamine and its receptors play an important role in the progression of various allergic diseases [26]. Notably, the histamine H1 receptor (H1 receptor) has been reported to regulate allergic lung responses; therefore, its

antagonists have been used to treat airway inflammation [27]. Beyond its role in mediating airway inflammation, our recent experimental work has identified that dectropine, a classical H1 receptor antagonist used to treat asthmatic symptoms, potently inhibits hepatitis E virus replication [28]. Along with our finding, a growing body of evidence also demonstrated that H1 receptor antagonists can inhibit various RNA virus infections [29][30].

## 2. Potential Anti-SARS-CoV-2 Mechanisms of H1 Receptor Antagonists

Preclinical data suggest that H1 receptor antagonists limit viral entry of Ebola/Marburg [31] or Hepatitis C virus (HCV) [32] even if the molecular pathways explaining these antiviral effects remain largely obscure. For example, diphenyl-piperazines (e.g., chlorcyclizine, cyclizine, and hydroxyzine), cycloheptene-piperidines (e.g., cyproheptadine, ketotifen, loratadine, and desloratadine), and phenothiazines (e.g., mequitazine and trimeprazine) have been found to inhibit HCV cell entry. Interestingly, the potential anti-HCV mechanisms of these drugs are likely independent of H1 receptor [33].

### 2.1. Intervention of Early Step of SARS-CoV-2 Infection

Consistent with HCV and Ebola, the H1 receptor antagonists may also inhibit SARS-CoV-2 infection via intervention in the early step of virus replication. It may prevent SARS-CoV-2 from entering the cell host through binding ACE2 [34]. Moreover, evidence showed that H1 receptor antagonists could inhibit SARS-CoV-2 infection through binding sigma receptor-1 (for hydroxyzine and diphenhydramine), an endoplasmic reticulum resident chaperone protein participating in early steps of SARS-CoV-2 replication [35][34]. Heparin belongs to glycosaminoglycan molecules which include heparan sulphate. During virus entry, SARS-CoV-2 spike protein was demonstrated to interact with both cellular heparan sulfate and ACE2 [16]. Therefore, disrupting the interaction between heparan sulphate and spike protein by exogenous and competitive heparin mimetics could limit the SARS-CoV-2 virus entering the cell, resulting in suppression of the inflammatory responses [36]. Histamine has been shown capable of binding to heparan sulfate [37][38]. It is interesting to investigate the involvement of heparan sulfate in the H1 receptor antagonist-mediated anti-SARS-CoV-2 activity.

Unlike H1 receptor, the proposed anti-SARS-CoV-2 mechanisms for H2 receptor antagonists are inhibition of Type 2 transmembrane serine protease (TMPRSS2) and 3-chymotrypsin-like protease (3CLpro) by famotidine [39]. However, a recent study revealed that the principal mechanism of action of famotidine for relieving COVID-19 symptoms is attributed to its on-target effect on H2 receptor activity, and is likely independent of other histamine receptors determined by competition assay [14]. Most recently, molecular docking results suggest that famotidine and cimetidine inhibit SARS-CoV-2 replication through the inhibition of non-structural proteins, including NSP3, NSP7/8 complex, and NSP9 [40]. The modes of action of anti-SARS-CoV-2 activity of famotidine needs to be further clarified.

### 2.2. NF- $\kappa$ B-Mediated Antiviral Activity by H1 Receptor Antagonist

Activation of cellular inflammation was observed following histamine binding to H1 receptor. This activation was mediated by phospholipase C (PLC) [41], protein kinase C (PKC), and NF-κB signaling pathways [42]. Our recent experimental work demonstrated that dectropine could potently inhibit HEV replication. The anti-HEV effect of dectropine requires the inhibition of NF-κB activity and is likely dispensable of H1 receptor [28]. Interestingly, activation of NF-κB in lung epithelial cells was found to facilitate SARS-CoV-2 propagation, and H1 receptor antagonists were able to suppress the activation of NF-κB in lung epithelial cells [43][44]. The above evidence together prompts us to hypothesize that the potential mechanism by which H1 receptor antagonists inhibit SARS-CoV-2 may include their inhibitory effects on NF-κB [28]. Of note, H1 receptor antagonists can inhibit NF-κB through H1 receptor-dependent and -independent mechanisms [44]. The implication of H1 receptor and the NF-κB signaling pathway in a H1 receptor antagonists-mediated anti-SARS-CoV-2 effect is intriguing and needs to be further explored.

### 2.3. Other Potential Antiviral Mechanisms

The observation that H1 receptor antagonists exert antiviral effects, however, also fits well with recent observations that the action of H1 receptor in physiology is much broader than the conventional view that such action is mainly restricted to allergic inflammation. The endogenous histamine stimulates oleoylethanolamide biosynthesis in the liver via H1 receptor activation, regulating liver ketogenesis [45]. Epidemiological evidence as well as preclinical studies indicate that H1 receptor antagonists are associated with increased food intake, body weight, and obesity [46]. The H1 receptor was also shown to play a vital role in the control of cellular metabolism. Genetic deletion of H1 receptor in mice leads to increased abdominal adiposity and glucose intolerance [47]. Metabolism and immune responses are two fundamental biological processes that protect the cell host from viral infection. Interestingly, it has been proposed that H1 receptor can modulate innate immunity beyond its role in regulating allergic reactions [48]. Thus, the blockage of H1 receptor by its antagonists may affect the SARS-CoV-2 replication via mediation of the crosstalk between metabolism and immune responses.

## 3. Opportunities and Challenges

There are various advantages in the application of H1 receptor antagonists for the treatment of COVID-19. First, these drugs are relatively inexpensive and readily to be used. Second, although the chronic inflammation may not be the primary driver of pathology, using H1 receptor antagonists can improve patient outcomes due to its natural role in reducing inflammation. However, it also should be noted that the first-generation H1 receptor antagonists are not strictly selective for the H1 receptor. They contribute to a spectrum of dopaminergic and cholinergic reactions, resulting in significant adverse effects in the central nervous system due to their capability of penetrating the blood-brain barrier [49]. Moreover, they are able to regulate cardiac channels, leading to wide range of side effects, including sedation, insomnia, and hyperactivity [50]. Besides that, H1 receptor antagonists have been associated with an increase in seizure susceptibility [51]; therefore, H1 receptor antagonists in most cases are not recommended to be prescribed to COVID-19 patients with epilepsy or febrile seizures. Another factor that may hinder the clinical use of H1 receptor antagonists in COVID-19 is the impairment of innate immune responses by these drugs [52].

As mentioned above, both loratadine and desloratadine could inhibit SARS-CoV-2 infection. They are new-generation H1 receptor antagonists which are highly selective to H1 receptor with less central nervous system side effects. Besides their role in reducing lung inflammation induced by histamine, they can suppress a number of other inflammatory activities [53], which make them ideal medications for relieving the excess inflammatory response of COVID-19. Overall, with studies describing H1 receptor antagonists to be capable of treating viral diseases, recent findings take us one step closer to understanding the underlying antiviral mechanism and the advantages of the H1 receptor antagonists in the treatment of COVID-19. In the future, the use of H1 receptor antagonists as antiviral agents will further advance our understanding of how these agents work beyond their intrinsic effects on the histamine receptor, and bear potential implications for the real-world treatment of COVID-19 patients.

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