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Histamine H4 receptor is a potential target for COVID-19 treatment

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Abstract

Pulmonary fibrosis and cytokine storms are two major complications in COVID-19 patients that can decrease life quality after recovery and even cause death. Histamine H4 Receptor (H4R) antagonists prevent lung fibrosis and reduce TNF-α and IL-6 secretion in several immune-mediated diseases. T-helper cell 17 (TH17), which is an important inflammatory effector in COVID-19 pathogenesis, expresses H4Rs on its surface. The stimulation of these receptors results in IL-17 production and, subsequently, TNF-α and IL-6 secretion, tissue remodelling, and fibrosis. The compatibility of the clinical manifestations of COVID-19 with the H4R function pattern further supports this theory. According to the above content, Histamine 4 receptors could be a potential target for COVID-19 treatment. H4R antagonists should be evaluated in experimental in-vitro studies and randomized controlled trials in terms of their therapeutic and preventive effects in COVID-19 complications, severity progression, and mortality.

Keywords: COVID-19, Histamine, H4R, Histamine H4 receptor

Abbreviations / Acronyms:
2019-nCoV: Novel Coronavirus; **ARDS:** Acute Respiratory Distress Syndrome; **CCR6:** Chemokine Receptor 6; **COVID-19:** Coronavirus Disease 2019; **H4R:** Histamine H4 Receptor; **IL:** Interleukin; **MERS:** Middle East Respiratory Syndrome; **PCR:** Polymerase Chain Reaction; **SARS-CoV-2:** Severe Acute Respiratory Syndrome Coronavirus 2; **TGF-β:** Transforming Growth Factor Beta; **TH:** T-helper (cell); **TNF-α:** Tumor Necrosis Factor Alpha; **TNF-β:** Tumor Necrosis Factor Beta; **TRAF6:** Tumor Necrosis Factor Receptor (TNFR)-associated Factor 6; **WHO:** World Health Organization

1. Introduction

Coronaviruses are the family of viruses from the Nidovirus superfamily. The coronavirus family has three genera (alpha, beta, and gamma). These viruses can infect animals and many animal species (1). In December 2019, several clusters of unknown cases of pneumonia were reported in Wuhan, China; these cases were related to the seafood wholesale market (2). The novel coronavirus was discovered as the pathogen agent in these cases. ”Wuhan virus” was the original name of this pathogen, but it was officially named 2019-nCoV later, and the disease was later renamed coronavirus infection disease-19 (COVID-19) (3, 4). On December 27, 2019, three adult pneumonia patients were admitted to Wuhan Hospital in China. These patients had had close contact with the seafood wholesale market, and the presence of a novel coronavirus [2019-nCoV] was identified by direct PCR, whole-genome sequencing, and cultures in their Broncho alveolar-lavage fluid (5). Forty-one out of 59 cases with flu-like symptoms who were admitted to a hospital in Wuhan were infected with 2019-nCoV on Dec 31, 2019, and 15% of 41 infected patients died (6). The world health organization (WHO) had reported 1,051,635 confirmed COVID-19 cases and 56,985 related deaths worldwide as of April 4, 2020 (7).

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2. Clinical and laboratory presentation of COVID-19

2.1. Clinical presentations

COVID-19 mostly manifests as nonspecific signs and symptoms such as fever and fatigue at the beginning. Nonproductive cough, dyspnea, and bone pain are other common clinical findings in COVID-19 patients; nausea and vomiting, abdominal pain, diarrhea, headache, and dizziness are uncommon symptoms (8). Severe COVID-19 patients present neurologic symptoms, such as headaches, vomiting, and loss of consciousness (9). About 20% of COVID-19 patients present cutaneous manifestations, such as erythematous rash and urticaria (10, 11).

2.2. COVID-19 and lung fibrosis

Ground-glass opacities and consolidations are major findings in COVID-19 patients' chest CTs, which can indicate vascular enlargement (12). Interlobular septal thickening and air-bronchogram are other common findings (8, 12, 13). Histopathological examinations of lung biopsy tissues have revealed diffuse alveolar damage (12, 14). Denuded alveolar lining cells with reactive type II pneumocyte hyperplasia were noted, and intra-alveolar fibrinous exudates were present alongside loose interstitial fibrosis and chronic inflammatory infiltrates (12, 14). Intra-alveolar loose fibrous plugs of organizing pneumonia were found to accompany intra-alveolar organizing fibrin in most foci (12). Pulmonary fibrosis is the most important factor that decreases Severe Acute Respiratory Syndrome (SARS) survivors' quality of life through pulmonary dysfunction after recovery. Plenty of studies confirm that pulmonary fibrosis is one of the most important complications in COVID-19 patients (15, 16).

2.3. Cytokine storms and immune dysregulation

COVID-19 and some other diseases, such as rheumatoid diseases, infectious diseases, and tumor immunotherapy, can cause the extreme release of pro-inflammatory cytokines (known as a cytokine storm [CS]), which results in multiple organ failure (17). The CS promoted by COVID-19 can lead to acute lung injury, acute respiratory distress syndrome (ARDS), and death, as well as SARS and the Middle East Respiratory Syndrome (MERS) (18). In a study on 41 patients, the results of plasma cytokine analysis confirmed that IL-1, IL-7, IL-8, IL-9, and IL-10 levels increased significantly, and IL-2, IL-17, IL-10, and TNF-α increased in severe patients (6, 19). Several studies have reported that the level of IL-6 was higher in critically ill and non-survivor patients than in others (20-22). In a study of 452 patients with COVID-19, 286 were diagnosed as having a severe infection. Severe cases had higher leukocyte counts and lower lymphocyte counts than other patients, which this decrease was significant in helper and suppressor T cells and a decrease in the number of T cells was more prominent in severe patients (23). In COVID-19 patients, lymphopenia is demonstrated as an important severity index, and one of the most probable mechanisms of lymphopenia is lymphocyte apoptosis caused by IL-6 and TNF-α (8, 24, 25).

3. Histamine

Histamine acts through four receptors [H1R, H2R, H3R, H4R], and it affects several functions in the human body. Histamine and its receptors are known to act as important effectors in inflammatory conditions, such as asthma, allergies, and autoimmune diseases. According to the review on immunologic functions of histamine receptors by Branco AC and Yoshikawa FS, histamine h4 receptor [H4R] regulates TH1/TH2 differentiation, increases IL-17 production from T-helper cell 17 (TH17), and promotes IL6 production while decreasing IL12 levels (26). Evidence confirms that H4R plays a key role in lung fibrosis and cytokine excretion, two major pathogenesis aspects of COVID-19 (27-29), which are explained in the following sections.

3.1. Histamine 4 receptor and lung fibrosis

H4R is detected in bronchial smooth muscle cells, endothelial and epithelial cells, and human lung fibroblasts. All these cells play a role in the pulmonary inflammation process through IL6 production (30). In a study done on human fetal lung fibroblast cells, it has been shown that histamine can stimulate fibroblast migration (27). The study on bleomycine-induced lung fibrosis showed that the H4R antagonist JNJ-7777120 can prevent lung inflammation and lung fibrosis (28). In another study on bleomycine-induced lung fibrosis, there was a significant increase in IL-beta, TNF-α, and Transforming Growth Factor Beta (TGF- β) levels, and JNJ-7777120 reduced airway remodelling, bronchial-obstruction, and pulmonary fibrosis (31).

3.2. Histamine 4 receptors and cytokines

H4R antagonists can reduce TNF-α secretion in several immune-mediated diseases such as asthma, colitis, and dermatitis. It also decreases IL-6, IL-5, IL-4, IL10, IFN-γ, IL-17, PGD2, and LTB4 in asthma patients (32-34). Cowden and Challapalli have demonstrated that H4R antagonists can reduce TNF production and H4R stimulation, resulting in liver injury and lung inflammation in mice (32). It has been proposed that H4R antagonists can act as an

anti-arthritis agent by inhibiting inflammation via TNF reduction (35) and the release of TNF-α and IL-8 is mediated by H4R receptors in humans (36). H4R's interaction with tumor necrosis factor receptor (TNFR)-associated factor 6 (TRAF6) can reduce central nervous system inflammation induced by lipopolysaccharide (37). The inhibitory effect of H4R antagonists in colitis is mediated by TNF-α and myeloperoxidase reduction in rats (38). Furthermore, H4R antagonists can reduce dermal inflammation and pruritus by decreasing tissue cytokines, which results in dendritic cell migration decrease (39). A study on human mast cell H4R demonstrated that H4R induces the production of several pro-inflammatory cytokines, including TGF-β1, TNF-α, TNF-β, IL-16, IL-6, IL-3, and IL-10 (29). Also, H4R stimulation can increase chemokine expression in human natural killer cells (40). H4R stimulation also decreases IL12, which was not determined to be high in studies on COVID-19 cytokine storms (6, 30, 39, 41).

4. TH17: The link between COVID-19 and histamine 4 receptor

IL-17 is a major inflammatory effector that induces granulopoiesis and the recruitment of neutrophils by G-CSF induction. It also causes fever through TNF-α, IL1b, and IL-6 induction. It has a role in tissue damage and remodelling thorough matrix metalloproteinase induction (42, 43). IL-17 has a critical role in bleomycine-induced pulmonary fibrosis by neutrophil and TH17 induction, and IL-17 promotes pulmonary inflammation and lung fibrosis in a synergistic process with TNF-α by increasing pro-inflammatory and profibrotic gene expression (44). Moreover, there was a notable increase in the number of TH17 and CCR6 cells in severe COVID-19 patients (45). The rise in TH17 cells and the enhancement of pathways related to IL-17 have been demonstrated in MERS-COV, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2), and H1N1 influenza, and this pattern was associated with higher mortality and pulmonary morbidities (46-48). It has been proposed that the TH17 pathway plays a key role in COVID-19 cytokine storms and that this pathway is an important target for COVID-19 treatment (43). Human TH17 cells express H4R, which can be stimulated by H4R agonists and result in IL-17 production (49). The results of several studies demonstrate a decrease in IL-17 production from TH17 in mice and humans by the administration of H4R antagonists (49-52).

5. Clues

Additional clues confirming the relationship between COVID-19 and H4R are explained as follows.

5.1. Clue 1

Anorexia and Diarrhea are the most common symptoms among COVID-19 patients. Also, gastrointestinal (GI) bleeding is also reported in some cases (53). The expression of TNF-α mRNA by H4R results in Cisplatin-induced anorexia in mice and H4R antagonist inhibits this process completely (54). Histamine 4 receptor blockage in both genetic and pharmacologic methods results in an improvement in colitis signs (38, 55). The role of H4R in colitis induction may be a probable reason for COVID-19 diarrhea, but this theory requires more histological analysis (6, 26, 55).

5.2. Clue 2

Severe COVID-19 patients show neurologic symptoms such as headache, vomiting, and a loss of consciousness, and histamine receptors, [particularly H1R and H4R] promote nerve damage (6, 9, 26, 56-58).

5.3. Clue 3

About 20% of COVID-19 patients display cutaneous manifestations such as erythematous rash and urticaria (10). Urticaria eruption was reported as the first signs of COVID-19 in an asymptomatic 27-year-old female in France, and this sign has progressed to classic symptoms of COVID-19 disease in 48 hours (11) and these symptoms can be related to inflammatory effects of H4R in skin tissue (39).

5.4. Clue 4

A cluster of Kawasaki-like patients have been reported in April 2020 in Bergamo province, Italy; the city which is highly involved with COVID-19. The incidence of Kawasaki disease in this cluster is estimated to be 30-folds increased (59). Also, another group of 8 children with Kawasaki disease was reported in May 2020 in London, 7 of which were demonstrated to be infected by SARS-COV-2 (60). This condition has been named pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) (61). In recent studies on the Kawasaki disease, a significant increase in IL-17 and TH17 proportions is reported in patients, and the TH17 proportions have been demonstrated to be significantly up-regulated in immunoglobulin-resistant patients (62, 63). Another study on the Kawasaki disease patients confirmed a significant decrease in TH17 in patients after treatment

(64). According to the above content, the stimulatory effect of H4R on TH17 may be the probable link between COVID-19 and Kawasaki disease.

6. Hypothesis

According to the above contents, the author hypothesizes that H4R stimulation via SARS-COV-2 results in IL-17 expression (which is associated with cytokine release, and pulmonary fibrosis) and H4R stimulation by SARS-COV-2 directly trigger pro-inflammatory cytokine release from mast cells and NK cells, which leads to cytokine storms. The compatibility of H4R stimulatory effects with gastrointestinal, neurologic, and dermatologic signs and symptoms of SARS-COV-2 supports this hypothesis. The recent clusters of Kawasaki-like disease and the role of TH17 in Kawasaki disease are additional clues that confirm that H4R is a potential effector in COVID-19. The author also hypothesizes that H4R antagonist therapy in mild and moderate stages of COVID-19 (before cytokine storms occur) can decrease complications, disease severity progression, and mortality.

7. Examining the hypothesis

Toreforant (JNJ-38518168) is a selective H4R antagonist that is available in oral form. In the synovial biopsy study on rheumatoid arthritis patients, treatment by Toreforant decreased IL-17 levels in the synovial fluid (65). A 100-mg/day dosage of Toreforant is demonstrated to be safe and initially efficient. No life-threatening side effects have been reported; only a minimal reversible rise in serum creatinine has been demonstrated in patients treated by Toreforant. Despite this, Toreforant could not pass phase 2b clinical trials at a dosage of 30mg/day (66). Toreforant is available and safe, and its oral form can be used in patients suffering from diseases with a wide range of severity. Since no clinical study on H4R antagonist therapy on COVID-19 patients is published yet, the author proposes in-vitro studies and further randomized controlled trials on mild and moderate COVID-19 patients to assess the therapeutic and preventive effect of H4R antagonists on disease complications, severity progression, and mortality rate.

8. Conclusions

The COVID-19 pandemic started in December 2019 and is now a worldwide health disaster. Cytokine storms and pulmonary fibrosis are two major complications associated with COVID-19. These complications are closely associated with TH17, and the stimulatory effect of H4R on TH17 has been confirmed in several studies. H4R can stimulate cytokine production directly; through the TH17 pathway and H4R blocking, it can prevent bleomycine-induced pulmonary fibrosis in murine models. Other matters supporting this theory are the compatibility of gastrointestinal, neurologic, and dermatologic signs and symptoms of COVID-19 with an H4R function pattern. In addition to the previous evidence, clusters of Kawasaki-like disease have recently been reported in some patients. These patients were highly infected with SARS-COV-2, and this can be explained by the important role of IL-17 in Kawasaki disease and the stimulatory effect of H4R on TH17. According to all evidence explained in this paper, the author hypothesizes that H4R plays an important role in COVID-19 pathogenesis and that it can be a potential target point for future studies on COVID-19 treatment and prevention. Due to the availability and safety of the human H4R antagonist, the author proposes in-vitro studies and further randomized controlled trials on the therapeutic and complication preventive effects of H4R antagonists in COVID-19 patients.

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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