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Review Article

Histamine 4 receptor is a Potential Target for COVID-19 Treatment

Mirmazloomi SR*

Qazvin University of medical science, Bahonar Blvd. Qazvin province, Iran

ABSTRACT

COVID-19 pandemic started in December 2019, and is a worldwide health disaster today, pulmonary fibrosis and cytokine storm are two major complications in COVID-19 patients which can decrease life quality after recovery, and cause death. Histamine effects on the immune system through 4 histamine receptors. The function pattern of histamine 4 receptor has many similarities to COVID-19 pathogenesis pattern.H4R antagonists prevent lung fibrosis in bleomycine-induced lung fibrosis murine models, it can reduce TNF-α and IL-6 secretion in several immune-mediated diseases such as asthma, colitis and dermatitis.H4R stimulation also decreases IL-12 which is not detected to be high in COVID-19 patients.TH- 17 acts as an important inflammatory effector in COVID-19 pathogenesis, through IL-17 secretion which results in TNF-α and IL-6 secretion, and also IL-17 promotes tissue remodeling and fibrosis via matrix metalloproteinase induction.TH-17 expresses H4R which can be stimulated by H4R antagonist and results in IL-17 production, this process can explain the relation between H4R and COVID-19 pathogenesis. The other content supporting this theory is the compatibility of gastrointestinal, neurologic, and dermatologic signs and symptoms of COVID-19 with the H4R function pattern.in addition to the previous evidences, clusters of Kawasaki-like disease are reported recently, these patients were highly infected with SARS- COV2, and this can be explained by the important role of IL-17 in Kawasaki disease and the stimulatory effect of H4R on TH-17. According to the above content the author hypothesis that H4R stimulation by SARS-COV2 results in IL-17 expression which is associated with cytokine release, and H4R is a potential target point for COVID-19 treatment. This hypothesis can be evaluated by a clinical trial study of the therapeutic and preventive effect of H4R antagonists in COVID-19 patient's complication, severity progression, and mortality.

Keywords: COVID-19; Histamine; H4R; Histamine 4 receptor

INTRODUCTION

Coronaviruses are the family of the viruses from the Nidovirus superfamily. Coronavirus family has three genera named alpha, beta, and gamma these viruses can infect many species of animals and humans in December 2019, several clusters of unknown cause pneumonia have been reported in Wuhan, China which were related to seafood wholesale market. The novel coronavirus demonstrated to be the pathogen agent in those cases. the "Wuhan virus" was the original name of this pathogen, but it was officially named 2019-nCoV later, and the disease was named coronavirus infection disease-19 (COVID-19. Three adult patients were admitted by pneumonia on December 27, 2019, in Wuhan hospital in china which had close contact with the seafood wholesale market and the presence of novel coronavirus [2019-ncov] was identified by direct PCR, whole-genome sequencing and culture in their Broncho alveolar-lavage fluid [1-5].

41 Of 59 cases with flue 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 expired(6) World health organization [WHO] has reported 1051635 confirmed COVID-19 cases and 56 985 deaths caused by NCOV-2019 worldwide until April 4, 2020.

CLINICAL PRESENTATIONS

COVID-19 mostly presents with nonspecific signs and symptoms such as fever and fatigue at the beginning; nonproductive cough, dyspnea, and bone pain are also common clinical findings in these patients while nausea and vomiting, abdominal pain, diarrhea, headache and dizziness are uncommon presentations in COVID-10 patients [6-8].

COVID-19 AND LUNG FIBROSIS

Ground-glass opacities and consolidations are major findings in COVID-19 patients chest CT which can present with vascular enlargement. Also, interlobular septal thickening and air-bronchogram are other common findings. Histopathologic examination of lung biopsy tissues revealed diffuse alveolar damage. Denuded

Correspondence to: Seyyed Reza Mirmazloomi, Qazvin University of medical science, Bahonar Blvd. Qazvin province, Iran; E-mail: Drrezamirmazloomi@gmail.com

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alveolar lining cells, with reactive type II pneumocyte hyperplasia, were noted Intra-alveolar fibrinous exudates were present along with loose interstitial fibrosis and chronic inflammatory infiltrates. Intra-alveolar loose fibrous plugs of organizing pneumonia were noted with the presence of intra-alveolar organizing fibrin seen in most foci pulmonary fibrosis is the most important factor decreasing quality of life by pulmonary dysfunction in SARS survivors after recovery. Plenty of studies confirm this fact that pulmonary fibrosis is one of the most important complications in COVID-19 patients [9-11].

CYTOKINE STORM AND IMMUNE DYSREGULATION

The COVID-19 and some other diseases such as rheumatoid diseases, infectious diseases, and tumor immunotherapy can cause extreme release of pro-inflammatory cytokines which is called cytokine storm [CS], which results in multiple organ failure. the CS promoted by COVID-19 can lead to acute lung injury, acute respiratory distress syndrome [ARDS] and death as well as severe acute respiratory syndrome [SARS] and the Middle East respiratory syndrome [MERS].In the study on 41 patients, the result of plasma cytokine analysis confirmed that IL-1, IL-7, IL-8, IL-9, and IL-10 levels had significant rise, and IL-2, IL-17, IL-10, and TNF levels were increased in severe patients. Several studies have reported that the level of IL6 in critically ill and non-survivor patients was higher in the study of 452 patients with COVID-19, 286 were diagnosed as severe infection. Severe cases had higher leukocyte count and lower lymphocyte count 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 in COVID-19 patients, lymphopenia is demonstrated to be an important severity index, and one of the most probable mechanisms of lymphopenia is lymphocyte apoptosis caused by IL6 and TNF- [12-14].

HISTAMINE

Histamine acts through 4 receptors [H1R, H2R, H3R, H4R] and it affects several functions in the human body. Histamine and its receptors are known to act an important effector in inflammatory conditions such as asthma, allergy, and autoimmune diseases .regarding to the review on immunologic functions of histamine receptors by Branco AC, Yoshikawa FS, histamine 4 receptor [H4R] regulates TH1/TH2 differentiation, increases IL17 production from TH17 and, promotes IL6 production and also decreases IL12 level. There are evidences which confirms that H4R plays a key role in lung fibrosis and cytokine excretion, two major pathogenesis aspects of COVID-19 which are explained in the following [15-20].

H4R AND LUNG FIBROSIS

H4R is detected in bronchial smooth muscle cells, endothelial and epithelial cells and human lung fibroblasts and all these cells play a role in pulmonary inflammation process by IL6 production In the study which has done on human fetal lung fibroblast cells, it has been approved that histamine can stimulate fibroblast migration]. the study on bleomycin-induced lung fibrosis showed that the H4R antagonist JNJ7777120 can prevent lung inflammation and lung fibrosis In another study on bleomycin-induced lung fibrosis there was a significant increase in IL-beta, TNF- and TGF-beta levels and JNJ7777120 reduced airway remodeling, bronchial-obstruction and pulmonary fibrosis.

H4R AND CYTOKINES

H4R antagonist can reduce TNF- secretion in several immune-mediated diseases such as asthma, colitis and dermatitis and also decreases IL6, IL-5, IL-4, IL10, IFN, IL-17, PGD2 and LTB4 in asthma. Cowden and Challapalli have demostrated that H4R antagonist can reduce TNF production and H4R stimulation results liver injury and lung inflammation in mice it has been proposed that H4R antagonist can act as an anti-arthritis agent by inflmamation inhibition via TNF reduction and the release of TNF- and IL-8 is mediated by H4R receptor in human H4R interaction with Tumor Necrosis Factor Receptor-Associated Factor 6 can reduce Central nervous system inflammation induced by Lipopolysaccharide the inhibitory effect of H4R antagonist in colitis is mediated by TNF- and myeloperoxidase reduction in rat and also H4R antagonist can reduce dermal inflammation and pruritus by decreasing tissue cytokines which results in dendritic cell migration decrease the study on human mast cell H4R demonstrated that H4R induces production of several pro-inflammatory cytokines including TGF-1, TNF-, TNF-, IL-16, IL-6, IL-3, IL-10 and also H4r stimulation can increase chemokine expression in human Natural Killer cells (36)H4R stimulation also decreases IL12 which is not determined to be high in studies on COVID-19 cytokine storm

TH17, THE LINK BETWEEN COVID-19 AND H4R

IL17 is a major inflammatory effector, it induces granulopoiesis and recruitment of neutrophils by G-CSF induction, it causes fever through TNF-, IL1b, and IL6 induction. It has a role in tissue damage and remodeling thorough matrix metalloproteinase induction IL17 has a critical role in bleomycin- induced pulmonary fibrosis by neutrophil and TH17 induction, and also IL17 promotes pulmonary inflammation and lung fibrosis in a synergistic process with TNF- by increasing proinflammatory and profibrotic gene expression and there was a notable increase in the number of TH17 and CCR6 cells in severe COVID-19 patients the rise of TH17 cells and enhancement of pathways related to IL17 has been demonstrated in MERS-COV, SARS-COV and H1N1 influenza and this pattern was associated with higher mortality and pulmonary morbidities and it has been proposed that TH17 pathway plays a key role in COVID-19 cytokine storm and this pathway is an important target for COVID-19 treatment. Human TH17 cells express H4R which can be stimulated by H4R agonist and result in IL17 production and the results of several studies demonstrated the decrease in IL17 production from TH17 in mouse and human by H4R antagonist administration

OTHER CLUES

There are also more clues confirming the relations between COVID-19 and H4R which they are explained as follows:

clue1. Anorexia and Diarrhea are the most common symptoms on COVID-19 patients and Gastrointestinal bleeding is also reported in some cases the expression of TNF- mRNA by H4R results in cisplatin- induced anorexia in mice, and H4R antagonist inhibits this process completely. Histamine 4 receptor blockage in both genetic and pharmacologic methods results in the improvement in colitis signs the role of H4R in colitis induction may be the probable reason for COVID-19 diarrhea, but this theory needs more histological studies clue2. Severe COVID-19 patients present neurologic symptoms such as headache, vomiting, and loss of

consciousness, and Histamine receptors, [particularly H1R and H4R] promote nerve damage clue3.about 20% of COVID-19 patients present cutaneous manifestations such as erythematous rash and urticaria urticaria eruption was reported as the first signs of COVID-19 in asymptomatic 27-year-old female in France, and this sign has progressed to classic symptoms of COVID-19 disease in 48 hours and these symptoms can be related to inflammatory effects of H4R in skin tissue.

HYPOTHESIS

According to the above contents, the author hypothesis that H4R stimulation by SARS-COV2 results in IL17 expression which is associated to cytokine release, and pulmonary fibrosis; and also H4R stimulation by SARS-COV2, directly triggers pro-inflammatory cytokine release from mast cells and NK cells which leads to cytokine storm; and the compatibility of H4R stimulatory effects with gastrointestinal, neurologic, and dermatologic signs and symptoms of SARS-COV2 is supporting this hypothesis. The recent clusters of Kawasaki like disease and the role of TH17 in Kawasaki disease is another clue which confirms that, H4R is a potential effector in COVID-19. The author also hypothesis that H4R antagonist therapy in mild and moderate stages of the disease [before cytokine storm] can decrease COVID-19 complications, disease severity progression, and mortality.

TESTING THE HYPOTHESIS

Toreforant (JNJ-38518168) is a selective Histamine 4 receptor antagonist which is available in oral form. In the Synovial Biopsy Study on Rheumatoid arthritis patients, treatment by Toreforant decreased IL17 levels of synovial fluid. The 100mg/day dosage of Toreforant is demonstrated to be safe and initially efficient, and no life-threatening side effects are reported, only the minimal reversible rise in serum creatinine has been demonstrated in patients treated by Toreforant. Despite all, the Toreforant couldn't pass phase 2b clinical trial in 30mg/day dosage Toreforant is available and safe, and the oral form can be used in patients with a wide range of severity. Since no clinical study on H4R antagonist therapy on COVID-19 patients is published yet, the author proposes the future clinical trial study on mild and moderate COVID-19 patients, to declare the therapeutic and preventive effect of H4R antagonist, on disease complications, severity progression and mortality rate.

CONCLUSION

COVID-19 pandemic is started in December 2019 and, is a worldwide health disaster now. Cytokine storm and pulmonary fibrosis are two major complications of COVID-19, these complications are closely associated with TH-17, and the stimulatory effect of H4R on TH-17 is confirmed by several studies.

H4R can stimulate cytokine production directly, and through the TH-17 pathway, and H4R blocking can prevent pulmonary bleomycine-induced fibrosis in murine models. The other content supporting this theory is the compatibility of gastrointestinal, neurologic, and dermatologic signs and symptoms of COVID-19 with the H4R function pattern.in addition to the previous evidences, clusters of Kawasaki-like disease are reported recently, these patients were highly infected with SARS-COV2, and this can be explained by the important role of IL-17 in Kawasaki disease and the stimulatory effect of H4R on TH-17. According to all pieces of evidence explained in the paper, the author hypothesis that H4R plays an important role in COVID-19 pathogenesis, and it can be a potential target point for future studies on

CONCLUSION

COVID-19 treatment and prevention. Due to the availability and safety of the human H4R antagonist, the author proposes a future clinical study on therapeutic and complication preventive effects of H4R antagonists in COVID-19 patients clue4. The 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 estimated to be 30-folds increased, and another group of 8 children with Kawasaki disease was reported in May 2020 in London, which 7 of them demonstrated to be infected by SARS-COV2(59), this condition has named paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) by the Royal College of Paediatrics and Child Health in recent studies on Kawasaki disease the significant increase in IL17 and TH17 proportions are reported in patients, and the TH17 proportions have been demonstrated to be significantly upregulated in Immunoglobulin-resistant patients another study on Kawasaki disease patients confirmed the significant decrease in TH17 in patients after treatment according to the above content, the stimulatory effect of H4R on TH17 may be the probable link between COVID-19 and Kawasaki disease.

CONFLICT OF INTEREST

There is no conflict of interest to declare

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