Histamine release theory and roles of antihistamine in the treatment of cytokines storm of COVID-19

Omar Abdelhay Eldanasory[1], Khalid Eljaaly, PharmD[2,3], Ziad A. Memish, MD[4,5,6] and Jaffar A. Al-Tawfiq[7,8,9*]

[1]Lecturer of neurosurgery, Al-Zahraa Hospital AL-Azhar University Faculty of medicine, Cairo, Egypt, [2]Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia; [3]College of Pharmacy, University of Arizona, Tucson, AZ; [4]Director Research Center, King Saud Medical City, Ministry of Health, [5]Al-Faisal University, Riyadh, Saudi Arabia; [6]Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, GA, USA5, [7]Specialty Internal Medicine and Quality Department, Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia, [8]Indiana University School of Medicine, Indianapolis, IN, USA, [9]Johns Hopkins University School of Medicine, Baltimore, MD, USA

Address Correspondence to:

Dr. Jaffar A. Al-Tawfiq*

P.O. Box 76; Room A-428-2, Building 61, Dhahran Health Center,

Johns Hopkins Aramco Healthcare, Dhahran 31311, Saudi Arabia.

E-mail address: jaffar.tawfiq@jhah.com; jaltawfi@yahoo.com

Tel: +966-13-870-3524; Fax: +966-13-870-3790

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To the Editor,

In a recent study, authors described therapeutic options for Coronavirus Disease-19 (COVID-19) [1]. Histamine is an endogenous biogenic amine distributed ubiquitously in the body and is present in high concentrations in the lungs, skin, and gastrointestinal tract. It acts as a local mediator in the immune system. Histamine brings about complex physiologic changes, including chemotaxis, cytokine production, and gastric acid secretion. These biologic changes occur via four G protein–coupled receptor (GPCR) subtypes: H_1 receptor (H1R), H_2 receptor, H_3 receptor, and H_4 receptor (Table 1). H1R is expressed in various cell types, such as neurons, endothelial cells, adrenal medulla, muscle cells, hepatocytes, chondrocytes, monocytes, neutrophils, eosinophils, dendritic cells (DCs), T cells, and B cells. H1R activation leads to activation of Th1 lymphocytes, and decreased humoral immunity. H2R is expressed by parietal cells of the gastric mucosa, muscle, epithelial, endothelial, neuronal, hepatocyte, and immune cells. H2R antagonizes some of the effects mediated by H1R and leads to the relaxation of smooth muscle cells, causing vasodilation. In a murine lung inflammation model, H2R loss has an effect on invariant natural killer T (iNKT) cells, aggravating local inflammation [2]**.**

H3R functions were identified in the central nervous system and peripheral and presynaptic receptors to control the release of histamine and other neurotransmitters. H4R is preferentially expressed in the intestine, spleen, thymus, bone marrow, peripheral haematopoietic cells, and cells of the innate and adaptive immune systems. Expression of H4R is regulated by stimulation with TNF-α, IL-6, IL-10, and IL-13, leading to inhibition of cAMP accumulation and activation of mitogen-activated protein kinases (MAPK) by H4R.

So histamine is a potent inflammatory mediator, commonly associated with allergic reactions, promoting vascular and tissue changes and possessing high chemoattractant activity. The use of selective H4R ligands and/or modulation of H1 and H4 receptor synergism may be more effective in the treatment of inflammatory conditions of the lung. Histamine also modulates the inflammatory response by acting on other cellular populations, in human lung macrophages. The binding of histamine to H1R induces production of proinflammatory cytokine IL-6 and β-glucuronidase**.** Blocking H4R in a model of pulmonary fibrosis alleviates the inflammatory response, reducing COX2 expression and activity, leukocyte infiltration, production of TGF-β (profibrotic cytokine), and collagen deposition**.**

To date a few studies looking into the use of antihistamine products in patients with COVID-19. In self-administered high dose oral famotidine therapy, all 10 patients had marked improvements of COVID-19 symptoms [3]. Interestingly, analysis of pharmacokinetic parameters of famotidine might indicate that it needs to be given intravenously to be effective in COVID-19 treatment given its low gastrointestinal absorption and volume of distribution [4]. In propensity-score matched retrospective cohort study comparing famotidine cohort (84 patients) to non-famotidine cohort (1536 patients), a crude analysis showed that famotidine use was significantly associated with reduced risk for death and was independently associated with risk for death or intubation (adjusted hazard ratio (aHR) 0.42, 95% CI 0.21-0.85) [5]. The famotidine group received between 10-40 mg/day for a median of 5.8 days, and 72% received it orally [5]. One limitation to recognize is the risk of unmeasured confounders, particularly that sicker patients might be more likely to receive proton-pump inhibitors than H2R blockers. Although famotidine is an H2R antagonist and used mainly for peptic ulcer and gastroesophageal reflux, its potential benefit was attributed to binding and inhibiting the 3-chymotrypsin-like protease [4]. There is currently one

ongoing double-blind randomized controlled trial in New York evaluating the efficacy of high dose intravenous famotidine (360 mg/day) with standard of care for a maximum of 14 days in hospitalized COVID-19 patients [6]. The H2R antagonists class also includes ranitidine cimetidine, and nizatidine. In allergic reactions, the preferred antihistamines target H1R [4]. Currently, we could not find studies evaluating the efficacy of H1R blockers in COVID-19. Histamine is a main mediator that is being released by immune system and other cells as a result of virus invasions or activation. Histamine initiates abnormal immune response leading to cytokine storm and multi-organs failure. Thus, the use of antihistaminic medications could result in a significant immune modulation which may help in the treatment of cytokine storm of COVID-19. Future studies could compare H2R antagonists with those of steroid therapy in addition to the effect of combination therapy in relation to standard therapy.

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Table 1: Types and Functions of Different Histamine Receptors

	Expression in Cell Types	Function	Available studies in relation to COVID-19
Histamine 1 Receptor (H1R)	neurons, endothelial cells, adrenal medulla, muscle cells, hepatocytes, chondrocytes, monocytes, neutrophils, eosinophils, dendritic cells (DCs), T cells, and B cells	• activation of Th1 lymphocytes, and decreased humoral immunity	• none
Histamine 2 Receptor (H2R)	parietal cells of the gastric mucosa, muscle, epithelial, endothelial, neuronal, hepatocyte, and immune cells	• antagonizes some of the effects mediated by H1R and leads to the relaxation of smooth muscle cells, causing vasodilation. • inhibition of CXCL10,	• Observational studies [3][4][5] • Multi-site Adaptive Trials [6] •

		IL-12, and TNF-α stimulation of IL-10, which is likely associated with Th2 polarization	
Histamine 3 Receptor (H3R)	identified in the central nervous system and peripheral and presynaptic receptors	• control the release of histamine and other neurotransmitters	• none
Histamine 4 Receptor (H4R)	preferentially expressed in the intestine, spleen, thymus, bone marrow, peripheral hematopoietic cells, and cells of the innate and adaptive immune systems.	• Activation causes chemotaxis in mast cells and eosinophils, leading to accumulation of inflammatory cells and control of cytokine secretion • increased secretion of IL-31 by Th2 cells	• none