Hypothesis

The combination effects of theophylline and corticosteroids in COVID-19

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ABSTRACT

Late in 2019, the novel coronavirus disease (COVID-19) became pandemic. The disease has associated with severe inflammatory symptoms of the respiratory epithelial cells and the dysfunction of several organs of the body. Studies have shown that theophylline plays an important role in acute inflammation and has a synergistic effect on low therapeutic concentrations with corticosteroid drugs and amplifies anti-inflammatory effect of corticosteroids by activating histone deacetylase-2 (HDAC2), which decreases corticosteroid resistance by increasing the affinity of corticosteroid receptors to corticosteroid drugs. Therefore, theophylline could be considered as an adjunctive anti-inflammatory drug in combination with corticosteroids in the treatment of patients with COVID-19.

***Keywords*:** COVID-19; inflammation; theophylline; corticosteroid

INTRODUCTION

In December 2019, a new type of viral pneumonia spread to Wuhan, China, and became pandemic. This virus which is called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or COVID-19, infects human respiratory epithelial cells and causes inflammation [1]. In several lung diseases, including chronic obstructive pulmonary disease (COPD), cystic fibrosis, asthma, interstitial lung disease and acute

respiratory distress syndrome, the cause of pulmonary inflammation is increased synthesis of cytokines, chemokines, inflammatory mediators, inflammatory mediator receptors and adhesion molecules. The expression of these genes in the inflammatory response is regulated by transcription factors, including nuclear factor kappa B (NF-κB) and activator protein (AP)-1 in airways [2-4]. Another symptom of COVID-19 is an Upper Respiratory Infection (URI) that in the acute stages of the infection causes olfactory loss because of nasal swelling, mucosal edema, and inflammatory obstruction of the olfactory clefts [5]. Drugs such as oral corticosteroids, topical corticosteroids, theophylline, zinc sulfate, alpha-lipoic acid, carverine, vitamin A, ginkgo biloba, and minocycline have been recommended to treat patients' lost olfactory [5]. Among these drugs, theophylline, as a methylxanthine, has also been used for a long time in the treatment of chronic obstructive airway diseases, such as third-line therapy in COPD [6]. Theophylline is less commonly used as a bronchodilator due to its side effects than inhaled anticholinergic and β2 agonist drugs [7,8]. Theophylline in higher therapeutic concentrations (not clinically applicable) has anti-inflammatory and bronchodilator functions through various molecular mechanisms such as adenosine receptor antagonism (A1-, A2A-, A2B-receptors), inhibition of phosphodiesterase activity, inhibition of NF-κB, inhibition of phosphoinositide 3 kinase-δ, increased interleukin-10 expression, increased apoptosis of inflammatory cells, decreased poly (ADP-ribose) polymerase-1 [9]. However this drug, at low plasma concentrations, has significant anti-inflammatory effects in COPD [10]. In more severe pulmonary obstruction, clinical improvement is enhanced when theophylline is used with a long-acting inhaled β2 agonist [11]. Studies have shown that if theophylline is eliminated from the treatment regimen of an asthma patient with COPD, the symptoms of the disease worsen [12]. According to new studies on theophylline in patients with COPD steroid resistance, theophylline has a synergistic effect on low therapeutic concentrations with corticosteroid drugs and amplifies the anti-inflammatory effect of corticosteroids by activating Histone Deacetylases (HDACs), especially Histone Deacetylase-2 (HDAC2) in macrophages and peripheral lung, which reduces corticosteroid resistance by increasing the affinity of corticosteroid receptors to corticosteroid drugs [10]. The main inflammatory mechanism in asthma and COPD is triggered by the activation of several inflammatory genes through the NF-κB signaling pathway,

leading to an imbalance between the enzymes Histone Acetylase (HAC) and histone deacetylase. This imbalance in inflammation is in favor of histone acetylase and increases the expression of inflammatory genes. But in the anti-inflammatory process, with the consumption of corticosteroid drugs, HDAC2 enzymes are activated in inflammatory cells and the inflammation is suppressed [13,14]. Figure 1 depicts that to treat acute pulmonary inflammation induced by COVID-19, theophylline can be used as an amplifier of steroid drugs effects, by recruiting HDAC2 gene in inflammatory cells.

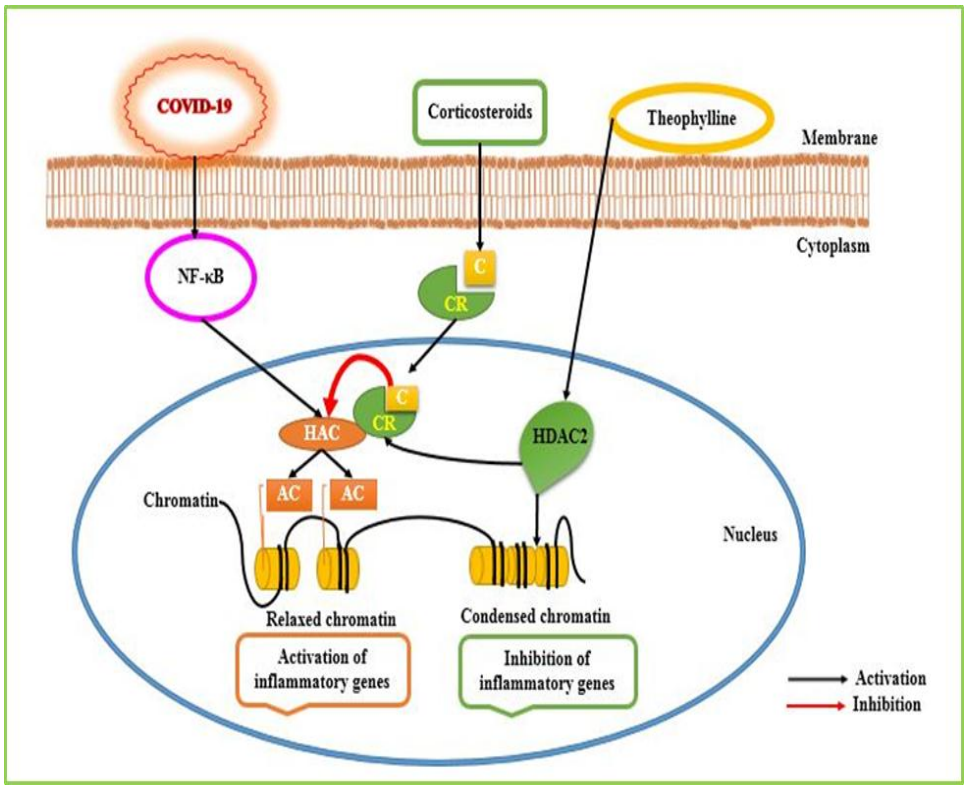

Figure 1. The main inflammatory mechanism of theophylline.
Abbreviations: COVID-19, Coronavirus disease 2019; NF-κB, Nuclear factor kappa B; CR, Corticosteroid receptor; C, Corticosteroid; HAC, Histone acetylase; HDAC2, Histone deacetylase; AC, Acetyl.

CONCLUSION

To treat inflammation in patients with COVID-19, theophylline has a synergistic effect with corticosteroid drugs and enhances the anti-inflammatory effects of corticosteroids (inhibition of HAC expression) by activating HDAC2.

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