BIBLIOGRAPHIC INFORMATION SYSTEM

Journal Full Title: Journal of Biomedical Research & Environmental Sciences

Journal NLM Abbreviation: J Biomed Res Environ Sci

Journal Website Link: https://www.jelsciences.com

Journal ISSN: 2766-2276

Category: Multidisciplinary

Subject Areas: Medicine Group, Biology Group, General, Environmental Sciences

Topics Summation: 128

Issue Regularity: Monthly

Review Process type: Double Blind

Time to Publication: 7-14 Days

Indexing catalog: Visit here

Publication fee catalog: Visit here

DOI: 10.37871 (CrossRef)

Plagiarism detection software: iThenticate

Managing entity: USA

Language: English

Research work collecting capability: Worldwide

Organized by: SciRes Literature LLC

Manuscript should be submitted in Word Document (.doc or .docx) through

Online Submission

form or can be mailed to support@jelsciences.com

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JOURNAL OF BIOMEDICAL RESEARCH & ENVIRONMENTAL SCIENCES
issn: 2766-2276
SUBJECT AREA(S): THERAPEUTICS
DOI: 10.37871

SHORT COMMUNICATION

The Possible Therapeutic Application of CO on COVID-19

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Summary

An outbreak of pneumonia caused by a novel Coronavirus (2019-nCoV) is ongoing in China [1]. The disease caused by 2019-nCoV was recently named as COVID-19 by WHO. Although the case-fatality rate of COVID-19 (about 2.3% up to now) is lower than SARS, they share many similarities [2,3]. Early studies have shown that increased pro-inflammatory cytokines were associated with pulmonary inflammation and extensive lung damage in SARS patients [4], while the latest report on COVID-19 showed that 2019-nCoV infection lead to high amounts of both Th1 and Th2 cytokines [5]. Moreover, ICU patients had higher levels of GCSF, IP10, TNFα, MCP1, IL2, IL7, IL10, MIP1A, suggesting the cytokine storm was associated with disease severity [5]. Corticosteroid therapy was frequently gave as a combined regimen for possible benefit by reducing inflammatory-induced lung injury. However, the drug is immunosuppressive and may delay viral clearance if given before viral replication is controlled [6], side-effects of corticosteroid also occurred in other cases [7]. Therefore, novel anti-inflammatory molecules could be considered in the treatment of COVID-19.

Accumulating evidence suggests a protective role of Carbon monoxide (CO), which is produced from the catabolism of heme *via* Heme oxygenase (HO), in the lungs and many other organ systems [8]. The anti-inflammatory properties of HO-1/CO has been demonstrated during pulmonary inflammation and lung injury through inhibiting Th17 cell-mediated immune response [9], suppressing NLRP3 inflammasome activation [10], decreasing the release of segmented neutrophils from the bone marrow [11], affecting PMN migration and improving microvascular permeability [12], while the inducers or stimulators varies from OVA, sepsis, LPS and oxidative stress [9-13]. CO was defined as novel Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) [14] that accelerates resolution of inflammation [15]. In this review, we will briefly summarize the anti-virus effects of CO, with an emphasis on its interaction with purinergic signaling.

Purinergic Signaling in Virus Infection

Increased levels of extracellular nucleotides were detected during virus infection such as Respiratory Syncytial Virus (RSV), parainfluenza virus and HIV [16-19]. By activating P2Y receptor-mediated signaling pathways, ATP

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DOI: 10.37871/jbres1687

Submitted: 13 February 2023

Accepted: 11 March 2023

Published: 12 March 2023

MEDICINE GROUP

THERAPEUTICS

VOLUME: 4 ISSUE: 3 - MARCH, 2023

How to cite this article: Rui-Gang Z. The Possible Therapeutic Application of CO on COVID-19. 2023 Mar 12; 4(3): 387-393. doi: 10.37871/jbres1687, Article ID: JBRES1687, Available at: https://www.jelsciences.com/articles/jbres1687.pdf

or UTP contributes to the accumulation of ions/fluid in the respiratory tract and reduction of Alveolar Fluid Clearance (AFC) [19,20]. The impaired AFC was due to suppressed Na^+ absorption and enhanced Cl^- secretion mediated by ATP or UTP during virus infection [19,21]. Interestingly, SARS-CoV spike protein and envelop protein transfected human airway epithelial cells (H441) cells showed decreased amiloride-sensitive Na^+ currents as well as ENaC protein level, indicating that lung edema in SARS infection may be partially due decreased levels and activity of ENaC at the apical surfaces of lung epithelial cells [22].

Apart from ion transport, purinergic signal also participates in host inflammatory responses during virus infection. Calven J, et al. [23] reported that Rhinovirus (RV) infected Bronchial Smooth Muscle Cell (BSMC) supernatants exhibited elevated ATP, Blocking of purinergic signaling with suramin inhibited BSMC expression of IL-33. Taken together, nucleotides participates in airway virus infection, therefore, purinergic signaling appears to be a new pharmacological target against virus [24].

Anti-purinergic Effects of CO

Apart from its well-defined anti-inflammatory effects, CO is also an emerging regulator of ion channels, modulating several classes of ion channels, including examples from calcium-activated K^+ (BK(Ca)), voltage-activated K^+ (K(v)) and Ca^{2+} channel (L-type) families, ligand-gated P2X receptors (P2X2 and P2X4), tandem P domain K^+ channels (TREK1) and the epithelial Na^+ channel (ENaC) [25]. Though there's no evidence demonstrating the direct effects of CO on Cl^- channels, it can regulate Cl^- transport in other ways. Extracelluar nucleotides are known to activate Cl^- secretion through either $[Ca^{2+}]_i$ or cAMP dependent pathway, contributing to the maintainess of Airway Surface Liquid (ASL) [26-30]. In lung diseases characterized by impaired oxygen and CO_2 transport, an increase in the ASL height, which is often observed during lung inflammation, might further aggravate the symptoms [31]. We've previously reported a inhibitory role of CO on P2Y receptor-mediated $[Ca^{2+}]_i$ increase and IP_3 formation [32]. Recently, by utilizing a simultaneous measurement combing electrophysiology and fluorescent, we further demonstrated that CO significantly suppressed UTP-evoked $[Ca^{2+}]_i$ increase and Cl^- secretion (Figure 1). We also tested the effect of CO on another important Cl^- secretion pathway by detecting intracellular cAMP and Cl^- secretion simultaneously [33]. Data revealed a strong inhibitory effect of CO on either $[Ca^{2+}]_i$ or cAMP dependent Cl^- secretion. Given that CO also directly suppress ENaC [34], we hypothesize that CO is a functional inhibitor against nucleotides-induced ion transport, and therefore can be used to alleviate edema.

Apart from modulating purinergic signaling mediated ion transport, HO-1/CO also reduced nucleotide-induced pro-inflammatory pathway activation, such as ERK1/2 MAPK as well as NF-κB, resulting in reduced IL-6 and IL-8 secretion [33,35].

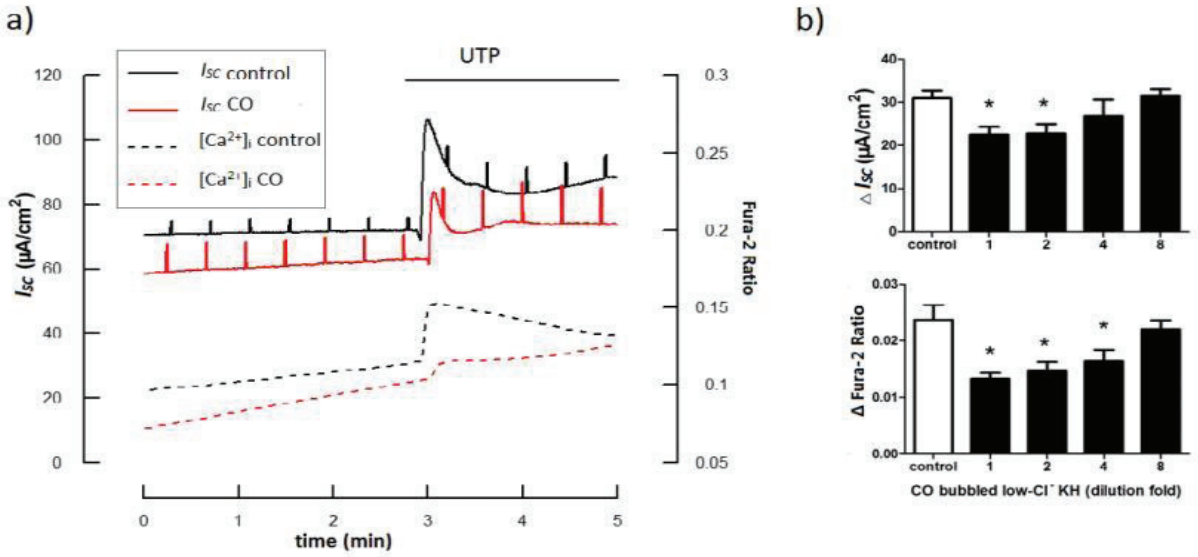

Figure 1 Electrospun nanofibers membrane of poly-ε-caprolactone visualization after 21 days of human Osteoblasts culture (Cells visualization in blue (nucleus /DAPI) and PLL^{FITC} labelled nanofibers in green): colonization and proliferation of osteoblasts into the nanofibers membrane.

Other Anti-virus Properties of CO

CO exerts its protective effect partially through modulating ROS production derived from either NADPH oxidase or respiratory chain [36,37]. It was reported CO plays a protective role in acute lung injury [38]. In an influenza virus infected mouse model, transfection of HO^{-1} resulted in suppression of both pathological changes and intrapulmonary hemorrhage; enhanced survival of animals; and a decrease of inflammatory cells in the lung [39]. Though CO could be produced by HO^{-1} *in vivo*, external CO can also induce the expression of HO^{-1}, further strengthen the effect of CO [40,41]. We also found an increased expression of HO^{-1} induced by CO releasing molecule 3 (data not published). HO^{-1} was found to suppress hepatitis C virus and dengue virus replication in biliverdin dependent manner [42,43]. A latest study showed that pre-treatment of A549 alveolar cell and primary cultures of Human Tracheal Epithelial (HTE) cells with relative low dose of CO (100 ppm) resulted in reduced RV14 titers in the supernatants and RV RNA levels in A549 and HTE cells, CO exposure also increased the expression levels of Interferon (IFN)-gamma mRNA and protein [44].

Coronavirus are enveloped virus that fuse with a host cell membrane in order to deliver their genome into the host cell. Specific cues in the endosomal microenvironment induce conformational changes in the viral fusion proteins leading to viral and host membrane fusion, acidification of the endosomal microenvironment is required for successful fusion and release of the viral genome into the cytoplasm, such as SARS-CoV [45], NL63 [46] and MERS-CoV [47]. In dendritic cells, HO^{-1} derived CO reduced cargo transport, endosome-to-lysosome fusion, and antigen processing, dampening the production of peptide-MHC complexes on the surface [48]. Tardif V, et al. [49] also demonstrated that CO significantly reduced the efficiency of fusion between late endosomes and lysosomes, therefore blocked antigen trafficking at the level of late endosome-lysosome fusion in dendritic cells. Whether HO^{-1}/CO has similar effect in the airway epithelial cells during virus infection remains unknown.

Additionally, CO is an important gaseous smooth muscle dilator [8] through activating PKG and/or BK(Ca) [50,51]. As previously described, COVID-19 patients showed higher inflammatory cytokine level [5], while many cytokines could facilitate bronchial smooth muscle contractility, including IL-17 [52], IL-4 [53], IL-13 [54], TNF-α [55]. Furthermore, some virus are capable of directly increase smooth muscle contraction. It was recently reported that RV infection lead to Airway Hyper Responsiveness (AHR) by increasing $[Ca^{2+}]_i$ mobilization [56]. Therefore, CO therapy not only provides anti-inflammation and anti-hypersecretion effect, but also alleviates airway narrowing. Together with its potential role in anti-virus infection, CO application may provide a comprehensive protective support to patients with COVID-19.

Safety and Clinical Trials of CO

The successful demonstration of CO-dependent protection in numerous animal models of disease has evoked the intriguing proposition that CO may be applicable as a molecular medicine in corresponding human disease states [57]. Exogenous administration of low concentration of CO by inhalation has been tested or currently in clinical trial to evaluate it's potential to reduce inflammation (NCT00094406), (NCT00122694), (NCT00531856). In a phase II clinical trial aimed to test the effect of inhaled CO on COPD, patients inhaled 2 hours of 100-125 ppm CO for 4 consecutive days showed reduced sputum eosinophils and improved responsiveness to methacholine. The median COHb reached after the fourth inhalation session of 100 ppm CO was 2.6%, with a highest individual value of 3.5%. After 125 ppm inhalation the median COHb was 3.1%, with the highest individual value reaching 4.5% [58], below the levels of COHb "achieved" with smoking of 20 cigarettes·day-1 where the 24-h average COHb levels reach 5.3% on average, with peaks >6% [59].

Remarks

CO is a potential candidate for therapeutic application during virus infected lung diseases. The unique advantage of CO is that it is an electroneutral gaseous molecule, which can diffuse easily across any membranes to exert its multiple function without interacting to unnecessary reactions like NO did [8,57,60,61]. Cytokine storm evoked by over-activated immune responses is a lethal characteristic during virus infection [62-64], CO could be a substitution of corticosteroid to control immune reaction and inflammation. CO can also alleviate ASL and alveolar fluid overproduction through either directly modulating ion channels or interacting with purinergic signaling pathways. Furthermore, CO and HO^{-1} showed potential anti-virus replication and

inhibits endosome fusion to prevent virus release, which is worthwhile further studies. Additionally, CO also protects host from oxidative stress as well as smooth muscle hypercontractility. The comprehensive effects of CO makes it a possible therapeutic support for virus infection-induced lung disease including the prevalent COVID-19.

Acknowledgment

The work was supported by the National Natural Science Foundation of China (Grant No.: 82000008) and GuangDong Basic and Applied Basic Research Foundation (Grant No.: 2019A1515110126).

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How to cite this article: Rui-Gang Z. The Possible Therapeutic Application of CO on COVID-19. 2023 Mar 12; 4(3): 387-393. doi: 10.37871/jbres1687, Article ID: JBRES1687, Available at: https://www.jelsciences.com/articles/jbres1687.pdf