



What about COVID-19 and arachidonic acid pathway?

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Abstract

Background and objective COVID-19 is a highly contagious viral disease. In this study, we tried to define and discuss all the findings on the potential association between arachidonic acid (AA) pathway and COVID-19 pathophysiology.

Methods A literature search across PubMed, Scopus, Embase, and Cochrane database was conducted. A total of 25 studies were identified.

Results The data elucidated that COX-2 and prostaglandins (PGs), particularly PGE₂, have pro-inflammatory action in COVID-19 pathophysiology. Arachidonic acid can act as endogenous antiviral compound. A deficiency in AA can make humans more susceptible to COVID-19. Targeting these pro-inflammatory mediators may help in decreasing the mortality and morbidity rate in COVID-19 patients.

Conclusions PGE₂ levels and other PGs levels should be measured in patients with COVID-19. Lowering the PGE₂ levels through inhibition of human microsomal prostaglandin E synthase-1 (mPGES-1) can enhance the host immune response against COVID-19. In addition, the hybrid compounds, such as COX-2 inhibitors/TP antagonists, can be an innovative treatment to control the overall balance between AA mediators in patients with COVID-19.

Keywords Arachidonic acid · COVID-19 · Prostaglandins · Leukotrienes · Eicosanoids · Thromboxane

Introduction

COVID-19 or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly contagious viral disease. Recently (April 30, 2020) we carried out a literature search for all published material on COVID 19 and arachidonic acid (AA) pathway. We searched PubMed, Scopus, Embase, and Cochrane databases using different relevant key words to identify all studies that address the association between COVID-19 and AA pathway. The following text words were used: “COVID19 and prostaglandin,” “COVID19 and thromboxane,” “COVID19 and leukotriene,” “COVID19 and lipoxin,” “COVID19 and 5-lipoxygenase,” “COVID19 and 12-lipoxygenase,” “COVID19 and 15-lipoxygenase,” “COVID19 and cytochrome P450 epoxygenase pathway,” “COVID19 and pro resolving lipid mediators,” and “COVID19 and NSAIDs.” Twenty-five studies were initially

identified. The purpose of this literature review is to synthesize the available information on the AA pathway involvement in COVID-19.

Arachidonic acid is a polyunsaturated fatty acid produced by membrane phospholipids through phospholipase-A₂ (PLA₂) in inflammatory condition. Das et al. suggested that AA can act as endogenous antiviral compound and can contribute to the inactivation of enveloped viruses, such as influenza virus, HIV, or SARS-CoV-2 [1]. The capacity to induce leakage or lysis of microbial cell membranes, to inhibit the respiratory activity, to uncouple the oxidative phosphorylation are some of the mechanisms responsible for the antimicrobial action of AA [1, 2]. Consequently, Das et al. suggested that T and B cells, leukocytes, macrophages, and other cells release AA when affected by viruses, such as SARS-CoV-2, and can inactivate the invading microorganisms [1]. Hence, a deficiency in AA can make humans more susceptible to SARS-CoV-2 [1].

AA can be a substrate for different pathways, such as cyclooxygenase (COX) and lipoxygenase (LOX) pathway, and can give rise to different mediators, which control inflammation. Prostaglandins (PG) and thromboxane (TXA₂) are pro-inflammatory lipid mediators produced through COX pathway. LOX gives rise to leukotrienes and lipoxins which

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possess pro- and anti-inflammatory activities, respectively. In contrast with these pro-inflammatory lipid mediators, other AA mediators, such as lipoxins, resolve inflammation and have potent anti-inflammatory activity [1]. There are different types of PGs (PGE₂, PGI₂, PGD₂, PGF_{2α}) which contribute to the inflammatory process.

Following viral infection, an activation of immune response occurs, which includes the release of inflammatory mediators, such as pro-inflammatory cytokines (IL-6, IL-1β, TNF-α) and eicosanoids (prostaglandins and leukotrienes) [3]. The second isoform of cyclooxygenase (COX-2) is responsible for producing the major part of PGs that are responsible for pain and inflammation [4]. Analogously, the SARS coronavirus responsible for the 2003 outbreak increased the production of PGs by binding to COX-2 [4]. Different studies have demonstrated that PGE₂ increases the viral pathogenicity in many viral infections such as CMV, RB, RSV, HSV, EV71, and CVB2 by interfering with the viral transcription translation and/or replication [3]. However, we should also consider that in some cases, such as in HBV and PIV3, PGE₂ can either stimulate or inhibit the viral pathogenicity [3]. Aso et al. reported that in human pulmonary microvascular endothelial cells, PGE₂ can play an upstream essential role in inflammation, leading to the increase of COX-2 expression, without affecting the COX-1 isoform, and increasing IL-8 [5].

Smeitink et al. suggested that PGE₂ has a significant role in COVID-19 pathophysiology hyperinflammatory and immune responses [3]; therefore, PGE₂ can be measured in patients with COVID-19. The same author also hypothesize that lowering the PGE₂ levels through inhibition of human microsomal prostaglandin E synthase-1 (mPGES-1) can enhance the host immune response against COVID-19 and moreover can be a promising therapeutic strategy for preventing severe disease progression and death. Moreover, mPGES-1 inhibition has the advantage of not effecting other PGs level and of allowing basal biosynthesis of PGE₂ by the two other constitutive synthases (cPGES and mPGES-2). Selective inhibition of mPGES-1 has been suggested as a therapeutic alternative to stimulate antiviral immunity in mice with influenza A virus (IAV). mPGES-1 inhibitors increased the survival of IAV mice [6]. Sonlicromanol (KH176; IUPAC chemical name (S)-6-hydroxy-2,5,7,8-tetramethyl-N-((R)-piperidin-3-yl)chroman-2-carboxamide hydrochloride) is a selective inhibitor of mPGES-1 that is currently under phase 2b study [7]. Sonlicromanol can attenuate the side effects of COX inhibitors.

In respect to gender differences, Pace et al. observed that in humans during acute inflammation, there was an increased expression of COX-2 and PGE₂ in males vs females [8]. Following these findings, it is possible that the increased PGE₂ levels in males can be one of the underline factors contributing to a more severe COVID-19 infection in males [3].

Moreover, other studies conducted in animals have reported that PGE₂ levels were affected by age [9], which can also be an underline factor of the hypersensitivity of older patients in respect to children with COVID-19 [3]. Considering that COVID-19 patients with comorbidities, such as obesity, have a higher risk of disease aggravation, PGE₂ may also contribute to the severity of the disease in these patients, considering that different studies have reported an increase of PGE₂ in obese patients [10]. In addition, PGE₂ can also contribute to intravascular thrombosis [11], which is another complication present in patients with COVID-19.

Isoprostanes are generated in vivo by free radical attack of AA. Reactive oxygen species (ROS) were found in plasma and lung tissue in patients with acute respiratory distress syndrome (ARDS), and the mPGES-1 selective inhibitor, sonlicromanol, showed radical scavenging activity and prevented ROS-driven cell death [12].

PGD₂ is another prostaglandin of interest for respiratory viruses. In an animal experimental model, infected with respiratory viruses, there was a higher production of PGD₂, which was further increased in older mice [13]. Vijay et al. suggested that PGD₂ has an important role in the lung inflammatory state by regulating different steps in the T cells responses in mice with SARS-CoV and MERS-CoV [13]. In addition, Werder et al. reported that PGD₂ production was increased in patients with severe syncytial virus (RSV) bronchiolitis, suggesting that DP agonists may be useful antivirals for the treatment of viral bronchiolitis and possibly as primary preventatives for asthma [14]. Moreover, 15d-PGJ₂, a PGD₂ derivative, which acts through DP1 receptor, has shown to reduce influenza morbidity and mortality in mice through PPARγ pathway [15]. Based on these findings, it would be of interest to measure the PGD₂ levels in COVID-19 patients.

PLA₂

Phospholipase A₂ group IID (PLA₂G2D) belongs to the phospholipases family and shows age-dependent increases in the lungs. Zheng et al. hypothesized that PLA₂G2D deficiency in myeloid cells plays an essential role in the formation of CD4 Tfh cells and humoral immune memory against respiratory coronavirus infection [16]. PLA₂ expression is also increased in HCV virus and is involved in HCV virus replication, making it a potential therapeutic target for anti-HCV therapy [17]. Other data suggested that CM-II-sPLA₂ is a potential alternative for the development of broad-spectrum antiviral drugs that target viral envelope lipid bilayers derived from the endoplasmic reticulum membrane [18]. Currently there are no data on the role of PLA₂ in COVID-19, and measuring its levels in these patients would not only fill this gap of knowledge but can give us further information on new therapeutic targets.

LOX pathway

Other than COX-2 and PGE₂, also 5-LOX pathway is involved in virus pathophysiology. Leukotrienes, especially LTB₄, inhibit influenza viral replication in vivo [19]. Influenza virus upregulates 5-LO in lungs of either infected animal models (mice) or humans [20]. LTB₄-treated neutrophils had enhanced virucidal activity against influenza virus, human coronavirus, and RSV [21]. In addition, higher levels of cysLTs observed in mice with influenza virus increased the survival rate [22]. Currently we did not identify any study on the implication of leukotrienes in COVID-19.

NSAIDs and COXIBs

NSAIDs block the cyclooxygenase enzymes (COX-1/COX-2), which are responsible for the production of inflammatory mediators (PG, LT, TX). Fang et al., while studying the severity of COVID-19 symptoms in patients with asthma and hypertension, linked the SARS-CoV-2 to the downregulation of angiotensin-converting enzyme-2 (ACE2), which instead is upregulated by ibuprofen [23]. Amici et al. reported that indomethacin, which is generally prescribed for treatment of gout and arthritis, inhibited human virus SARS-CoV replication at a concentration dose of 1 mg/kg [24]. However, different studies have questioned the role of NSAIDs and specifically of ibuprofen in patients with COVID-19. The reason behind that is that NSAIDs use in long term has been associated with several side effects, such as gastrointestinal and cardiovascular complications, nephrotoxicity, etc. Voiriot et al. reported that after respiratory tract infection, NSAIDs were associated with severe complications, such as respiratory tract infection and peritonsillar abscess [25]. NSAIDs inhibit COX; hence, they also inhibit the synthesis of anti-inflammatory AA mediators, specifically, lipoxins and resolvins, which lead to a delay of the resolution of the inflammation [25]. In line with this, Basille et al. showed that despite NSAIDs were taken for long term or for short term to treat acute illness, they were associated with respiratory complications [26].

But does this evidence also apply to COVID-19 pandemic? On March 2020, the French health authorities published a warning on the severe side effects of NSAIDs in patients with COVID-19 [27]. EMA has declared no evidence of NSAIDs and ibuprofen in COVID-19 worsening [28]. In line with this, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) reported that there is not a current research on ibuprofen and COVID-19 worsening [29]. Moreover, WHO suggests the use of ibuprofen as antipyretic drug and paracetamol as a first treatment option for fever or pain. Patients that take NSAIDs for different reason should not stop using them for fear of their COVID-19 risks [4].

Considering that NSAIDs can cause gastric side effects (ulcer, bleeding) or an increased risk of cardiovascular problems, which can be explained by a disbalance between AA mediators (prostacyclin and TX), the selective inhibition of mPGES-1 can be a better strategy in controlling inflammation in COVID-19. Das et al. suggested that also an intravenous or oral administration of AA can help in increasing the resistance, facilitating the recovery, or even preventing (higher AA levels) SARS-CoV-2 [1]. In addition we also hypothesize that dual compounds COX-2 inhibitors/TP antagonist, providing the anti-inflammatory effect and cardiovascular safety, may be an effective strategy in patients with SARS-CoV-2.

Concluding, we must not underestimate the importance of AA mediators in promoting or controlling inflammation in COVID-19; therefore, we believe that further studies on AA pathway implication in COVID-19 can contribute in developing new therapeutic strategies combating inflammation.

Author's contributions M.H is the only author of the manuscript who performed the literature search, drafted the manuscript, and reviewed the manuscript for its intellectual content.

Compliance with ethical standards

Conflict of interest The author declares that has no conflict of interest.

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