Could Palmitoylethanolamide Be an Effective Treatment for Long-COVID-19? Hypothesis and Insights in Potential Mechanisms of Action and Clinical Applications

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ABSTRACT

COVID-19 is highly transmissive and contagious disease with a wide spectrum of clinicopathological issues, including respiratory, vasculo-coagulative, and immune disorders. In some cases of COVID-19, patients can be characterized by clinical sequelae with mild-to-moderate symptoms that persist long after the resolution of the acute infection, known as long-COVID, potentially affecting their quality of life. The main symptoms of long-COVID include persistent dyspnea, fatigue and weakness (that are typically out of proportion, to the degree of ongoing lung damage and gas exchange impairment), persistence of anosmia and dysgeusia, neuropsychiatric symptoms, and cognitive dysfunctions (such as brain fog or memory lapses). The appropriate management and prevention of potential long-COVID sequelae is still lacking. It is also believed that long-term symptoms of COVID-19 are related to an immunity over-response, namely a cytokine storm, involving the release of pro-inflammatory interleukins, monocyte chemoattractant proteins, and tissue necrosis factors. Palmitoylethanolamide (PEA) shows affinity for vanilloid receptor 1 and for cannabinoid-like G protein-coupled receptors, enhancing anandamide activity by means of an entourage effect. Due to its anti-inflammatory properties, PEA has been recently used as an early add-on therapy for respiratory problems in patients with COVID-19. It is believed that PEA mitigates the cytokine storm modulating cell-mediated immunity, as well as counteracts pain and oxidative stress. In this article, we theorize that PEA could be a potentially effective nutraceutical to treat long-COVID, with regard to fatigue and myalgia, where a mythocondrial dysfunction is hypothesizable.

KEYWORDS: SARS-CoV-2, nutraceuticals, inflammation, abnormal immune response

COVID-19 is highly transmissive and contagious with a wide spectrum of clinicopathological issues, including respiratory, vasculo-coagulative, and immune disorders.[1] It has been suggested that SARS-CoV-2 binds by using glycoproteins expressed on its surface to the receptor of the angiotensin-converting enzyme 2 (ACE2), also known to be the SARS-CoV-2 functional receptor, which is distributed in the respiratory tract epithelium, lung parenchyma, and other areas, such as the gastrointestinal tract and endothelial cells.[2] In addition to ACE2 receptors, SARS-CoV-2 uses the serine protease type II transmembrane serine protease for spike protein priming. This protein binds to the ACE2 receptors that are expressed by mastocytes of the human cells.[3] Mast cells (MC) are strategically placed below the epithelial layer and closely associated with blood vessels. This location allows them to act as sentinels for tissue damage and pathogen invasion, as they interface with the external environment of the body, such as the skin, lung, and intestines.[4,5] Thus, MCs could play an important role in COVID-19's inflammation.[6]

It has been shown that in severe cases of general inflammation, there is a significant impairment of T-helper 1 (Th1) immune function (cell-mediated immunity); consequently, the immune system is forced to polarize towards a T-helper 2 (Th2) immune response (humoral immunity), whose effectors are mastocytes, basophils, eosinophils, and plasma cells.[7,8] This immunity over-response is known as a cytokine storm, involving the release of pro-inflammatory cytokines (e.g., interleukins [IL]-1, -6, -8, -17, and -1β, monocyte chemoattractant protein-1 [MCP-1], and tissue necrosis factor α [TNF-α]) that contribute to the rapid systemic organ failure observed in select critically ill patients, including those with COVID-19.[9]

In particular, respiratory infections begin with stimulation of innate immune response, signaling a cascade that starts with the recognition of pathogen-associated molecular patterns by pattern recognition receptors (PRRs), such as the toll-like receptors (TLRs) 3, 4, 7, and 8, which are expressed on several immune cells in the lung.[10] At the same time, other intracellular cytosolic PRRs, such as melanoma differentiation-associated protein 5 (MDA5) and retinoic acid-inducible gene I (RIG-I), are activated, as they are present in all cell types, including those of the lung.[11] Contemporarily, the innate immune system induces transcription factors in the nucleus, which, in turn, stimulate expression of types I and III interferons (IFNs) and other pro-

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inflammatory cytokines.[12]

Therefore, SARS-CoV-2 causes massive cell death and cellular debris that activates inflammasomes,[13] which in turn trigger a macrophage-derived eicosanoid storm and a surge of pro-inflammatory bioactive lipid mediators, such as prostaglandins and leukotrienes, that increase local inflammation, further inducing the cytokine storm.[14–17]

The SARS-CoV-2 outer surface consists of two other structural proteins, known as envelope and membrane proteins, and an important phospholipidic envelope, which derives from the cytoplasmatic membrane of the infected cell via budding. Because of the development of autoantibodies against this phospholipidic envelope (e.g., lupus anticoagulant, anti-cardiolipin, anti-β2glycoprotein), a serious antiphospholipid syndrome secondary to SARS-CoV-2 infection can occur, leading to arterial and venous thromboses in five percent of patients with COVID-19.[18]

Due to these mechanisms, SARS-CoV-2 infection causes a severe inflammatory response in the lungs, with interstitial mononuclear inflammatory lymphocytes infiltrating the lung.[19] The prolonged immunoparalytic and profibrotic state after hyperinflammation during SARS-CoV-2 infection leads to vulnerability to secondary infections and organ dysfunction, even after so-called recovery from the disease. This is why compounds that could counteract this dangerous inflammation are necessary.

On this basis, immunomodulatory therapies, such as checkpoint inhibitors, transforming growth factor β (TGF-β) inhibitors, hematopoietic growth factors, cytokines, and chemokines, are under investigation in this post-infectious setting. For example, TGF-β inhibitors might be used to neutralize or reverse immune suppression, as well as fibrosis, in post-sepsis/post-intensive care unit (ICU) syndromes.[20]

Recently, more attention has been given to phytotherapics and food supplements,[21,22] especially for endocannabinoid-related complexes, such as endogenous bioactive lipid amides, due to their pleiotropic homeostatic properties, including immune response regulation, control of food intake, neuroprotection, and inhibition of pain and inflammation.[23–25] Oleoylethanolamide (OEA), cannabidiol, palmitoylethanolamide (PEA), and other unsaturated fatty acids have all been put forward as promising drug candidates for potential treatment of the novel SARS-CoV-2 pandemic.[26–28] Particular attention has been given to PEA, a naturally occurring lipid mediator present in peanuts, fenugreek seeds, and soybean lecithin[30] that has an entourage effect, a mechanism by which cannabis compounds other than tetrahydrocannabinol (THC) act synergistically with it to modulate the overall psychoactive effects of the plant, on the endocannabinoid system,[31] while lacking the psychotropic side effects of cannabinoids, as a potential drug candidate. PEA can prevent MC-induced pulmonary inflammation and fibrosis during SARS-CoV2 infection,[31] but, due to its properties, the nutraceutical could be an alternative therapy for the long-term consequences of COVID-19.

WHY PEA COULD WORK IN LONG-COVID

Patients with COVID-19 can present with several symptoms, including fever, shortness of breath, cough, sore throat, nasal congestion, dizziness, chills, muscle ache, arthralgia, weakness, fatigue or myalgia, chest tightness, excessive mucus production with expectoration, hemoptysis, and dyspnea.[34,35] Severe or fatal complications include acute lung injury (ALI), acute respiratory distress syndrome (ARDS), sepsis, metabolic acidosis, septic shock, arrhythmia, acute cardiac injury, heart failure, acute kidney injury, bleeding, coagulopathy, hypotension, hypoperfusion, organ failure (also known as multiple-organ failure [MOF] or multiple-organ dysfunction syndrome [MODS]), and hypoxic encephalopathy and death.[34–36] Growing evidence demonstrates the involvement, both directly and indirectly, of SARS-COV-2 on the nervous system.[36]

In some cases, the patients with SARS-CoV-2 could be characterized by clinical sequelae with mild-to-moderate symptoms that persist long after the resolution of the acute infectious disease, termed long-COVID, or persistent post-COVID syndrome (PPCS), potentially affecting their quality of life. The appropriate management and prevention of potential PPCS sequelae has not been particularly supported. Post-COVID sequelae vary from patient to patient, and a consensus regarding the characterization of possible symptoms has not been reached.[35]

One hypothesis that accounts for the longstanding illness could be the inability to repress the inflammatory response, leading to long-lasting counterbalancing compensatory anti-inflammatory response syndrome, from the initial hyperinflammatory cytokine storm up to the progression to ARDS. This protracted, critical, chronic immunosuppression condition,[37–39] which is seen in post-sepsis patients, is one of the hypothesized causes of PPCS.[20]

PPCS includes persistent dyspnea, fatigue and weakness (that are typically out of proportion to the degree of ongoing lung damage and the degree of gas exchange impairment), persistence of anosmia and dysgeusia,[40] neuropsychiatric symptoms,[41] (including depression, anxiety, and psychosis),[42] nervous asthenia, post-traumatic stress disorder (PTSD), headache, insomnia, cognitive dysfunctions (brain fog, memory lapses), and delirium (sometimes due to an encephalitis). Bacterial and funginal co-infections, as well as thrombotic complications due to fulminant activation of coagulation and consumption of coagulation factors, might also occur.

Another potentially fatal sequelae is pulmonary fibrosis, which is commonly seen in follow-up imaging of recovered patients and which is different than interstitial pulmonary fibrosis.[41–45] Post-COVID fatigue and anhedonia are common after recovery from novel coronavirus infection[46] and are sometimes correlated to undiagnosed lung complications. Moreover, patients with COVID-19 commonly present with signs of myocardial injury, including heart failure, myocarditis, and/or exacerbation of existing cardiovascular disease.[47] The etiology is variable and could be due to pulmonary hypertension, overstimulation of the renin-angiotensin system, atherosclerotic plaque rupture via the action of proinflammatory cytokines, ACE2-mediated viral invasion of cardiomyocytes, myocardial oxygen supply/demand mismatch, or iatrogenic cardiotoxicity of potential anti-COVID-19 agents. In this heart/lung remodeling process, TGF-β might play a pivotal role.

In 1993, the Nobel Prize in Medicine winner, Rita Levi-Montalcini, provided scientific

evidence that PEA, an endogenous fatty acid amide that regulates lipid metabolism, downregulates hyperactive mastocytes in a dose-dependent manner, through a feedback mechanism defined as autacoid local inflammation antagonism (ALIA); for this reason, PEA is nicknamed ALIAmide.[50] PEA is an endogenous fatty acid amide able to bind the peroxisome proliferator-activated receptor-α (PPAR-α), also known as nuclear receptor subfamily 1 group C member 1 (NR1C1), a major regulator of lipid metabolism.[51] In addition, PEA shows affinity for vanilloid receptor 1 (VR1) and for cannabinoid-like G protein-coupled receptors 55 (GPR55) and 119 (GPR119),[52] enhancing anandamide activity by means of the entourage effect.[53,55] Due to its anti-inflammatory properties, PEA has been recently used as an early add-on therapy for patients with COVID-19. It is believed that PEA could mitigate the cytokine storm, avoiding stimulation of cell-mediated immunity, as do corticosteroids or tocilizumab.[56–58] PEA has a multitargeted action, and its potential anti-viral mechanisms might be related to several other signaling pathways, such as TLRs, PPAR-α, nitric oxide and cyclooxygenase-2 (COX2), and S100 calcium binding protein B (S100B) and glial fibrillary acidic protein (GFAP) signaling pathways.[59,61]

On the other hand, the anti-inflammatory properties of PEA are related to its ability to antagonize the nuclear factor-κB (NF-κB) signaling pathway via the selective activation of the PPAR-α receptors[59,62] that are predominantly expressed in tissues involved in fatty acids metabolism, such as liver, heart, kidney, and muscle, as well as on several types of immune cells, including undifferentiated monocytes, differentiated human macrophages, and T and B lymphocytes.[63] By the dual mechanism of PPAR-α antagonization of the NF-κB signaling pathway, through interacting with NF-κB p65 or upregulating the expression of inhibitors of NF-κB (IκBs),[64] PEA downstream regulates several genes involved in the inflammatory response, such as pro-inflammatory cytokines (tumor necrosis factor [TNF]-α, IL-1β), cell-adhesion molecules, and signal mediators, such as inducible nitric oxide synthase (iNOS), COX2, S100B, and GFAP.[65,66]

PEA has been utilized as an anti-inflammatory treatment for influenza and the common cold[67] because of these multiple actions, as well as because of its antinociceptive,[68] neuroprotective, and anticonvulsant properties.[69] At first, PEA (at a dosage of up to 1800mg/daily) was used to prevent respiratory tract infections and diminished the number of episodes of fever, headache, and sore throat on the mean duration of disability and fever, without side effects. This compound has been studied in a variety of animal and human models for a number of disorders, featured by overactive and dysfunctional hyperinflammation, such as osteoarthritis, traumatic brain injury, multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's disease, inflammatory bowel disease, asthma and allergic contact dermatitis, and spinal cord injury.[62,71–77]

Recently, Heide et al[78] reported that prophylactic intraperitoneal PEA administration in patients with meningitis significantly reduced the systemic concentration of two pro-inflammatory bioactive lipids, namely, arachidonic acid and 20-hydroxyeicosatetraenoic acid, leading to a decrease of vasospasm and other cerebrovascular alterations occurring in bacterial meningitis. In addition, the anti-inflammatory action of PEA has been used for intestinal inflammation in animals and inflammatory bowel disease by decreasing the expression and release of pro-inflammatory cytokines, as well as neutrophil and macrophage infiltration in sulfate-induced ulcerative colitis.[79,80]

Based on all this information, our hypothesis is that PEA may be administered either in acute phase of COVID-19 infection or in the persistent post-COVID syndrome to mitigate the SARS-CoV-2-induced inflammation. Indeed, chronic inflammation (with the persistence of cytokines and IL or other pro-inflammatory molecules) might be responsible not only for respiratory and coagulation complications, but also for the aspecific/subjective and persistent symptoms, including fatigue. Due to its complex mechanism of action, PEA could counteract the inflammatory process with a potential relief of the symptoms, including the subjective ones.

Recent studies suggest a potential autoimmune inflammatory pathogenesis rather than one driven by viral replication.[81] Whether this translates to all patients or to the mechanism(s) causing multiorgan involvement requires further research in patients with long-COVID. Fatigue and myalgia are among the most difficult symptoms to manage, not only in COVID-19, but also in non-COVID-19-related fatigue syndromes. Indeed, it has been shown that patients with COVID-19 still have high levels of fatigue and anhedonia after recovery from infection,[82] especially in the patients discharged from the hospital.[83] However, anti-inflammatory/antinociceptive drugs are known to be effective in treating such disorders, and this is why PEA could be considered the perfect candidate to treat the problem.

We hypothesize that fatigue and fybromyalgia in long-COVID could be comparable to chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME), a condition of unknown origin characterized by severe fatigue (lasting for more than 6 months) and some accompanying symptoms (e.g., muscle pain, post-exertional fatigue, headache, etc.) that leads to significant disability.[84,85] The etiology is still under debate,[86–89] although some studies showed elevation of some cytokines, such as IL-1α, IL-12, IL-23, and IL-8, as well as TGF-β and macrophage colony-stimulating factor 1 (CSF-1). Notably, increased concentrations of IL-12 and IL-23 have been especially associated with multiple sclerosis, in addition to psoriasis, inflammatory bowel disease, cancer, and rheumatoid arthritis.[90–92]

As previously specified, PEA has many anti-inflammatory properties, and, due to the reduction of oxidative/nitrosative stress, might prevent the endothelial damage that contributes to the pathogenesis of systemic inflammatory response in severe COVID-19,[93] and potentially in long-COVID as well. Since an increased release of IL-6 and IL-1β with the activation of NF-κB (which is involved in the overexpression of inflammatory cytokines adhesion molecules and chemokines) has been reported after SARS-CoV-2 infection,[94] we hypothesized that PEA could be used as a key element and mediator of the resolution of inflammatory processes, thus counteracting the progression of chronic inflammation and determining an effective response to the chronic pain and fatigue in long-COVID. The lack of drug interactions and absence of adverse effects recommend PEA as a promising

and innovative therapeutic strategy, while also taking into account the anti-inflammatory and neuroprotective adjuvant properties in the earliest stage of COVID-19.[70]

CONCLUSION

Available data suggest that PEA could be an optimal therapy to fight inflammation caused by COVID-19 by mitigating the cytokine storm in these frail patients without adverse events. Indeed, the compound has the advantage of not weakening, but positively modulating, cell-mediated immunity, as do immunosuppressive agents, such as corticosteroids or tocilizumab.[95]

In the present work, we discuss the sequential key immunological events that occur during SARS-CoV-2 infection and are involved in the immunophatogenesis of COVID-19. In particular, we discuss the excessive production of pro-inflammatory cytokines caused by COVID-19 that can lead to the development of the cytokine storm syndrome. This condition results in uncontrollable inflammation that can further impose MOF, eventually leading to death. Medical complications (e.g., fatigue, haedache, etc.) associated with SARS-CoV-2 infection are commonly reported in patients with long-COVID. This phenomenon is defined as not recovering for several weeks or months following the beginning of symptoms, and patients might present with chronic and recurrent fatigue for weeks and months after SARS-CoV-2 infection.[96,97] Understanding the effects and complications of long-COVID and how to manage it is the next challenge for public health services. There is an increasing need to understand the disease mechanisms and identify drug targets and inflammatory processes associated witn COVID-19.

In a recent work, Doykov et al[98] focused on medical complications associated with post-SARS-CoV-2 infection by evaluating changes in immune response associated proteins. They observed an increase in peroxiredoxin 3 (PRDX3) and carbamoyl phosphate synthetase I (CPS1), which both originated from the mitochondria. In particular, PRDX3 is a well-known antioxidant that seems to increase in the serum of patients infected with SARS-CoV-2, as it represents a persistent mitochondrial stress response, whereas CPS1 is a major mitochondrial urea cycle enzyme in hepatocells, and it is known to be cleared by peripheral blood mononucleal cells. The observed reduction in the serum of patients infected by SARS-CoV-2 might be related to enhanced circulation and activity of peripheral blood mononucleal cells. Given that it is hypothesizable that a mitochondrial dysfunction could be at the basis of fatigue and fibromyalgia, studies on this issue and compound potentially facing ossidative stress, similar to PEA, are welcomed. Furthermore, serum levels of other proteins, such as cystatin C and progranulin, appeared altered in patients after 40 days post-infection, even in patients who had suffered from asymptomatic or mild SARS-CoV-2 infection, showing a persistent inflammatory response patients with long-COVID. PEA could be used to fight this abnormal response.

Indeed, as previously affirmed, PEA has positive therapeutic effects, both on inflammatory processes and on oxidative stress. PEA could be a valid alternative to the use of anti-inflammatory drugs, or, at least, a possible therapy that works in synergy with them. It showed considerable versatility in counteracting inflammation in all its formulations and derivatives and also in association with other natural antioxidant molecules, such as flavonoids. However, it is important to evaluate the exact therapeutic doses and protocols.

In conclusion, we believe that, with its widely anti-inflammatory, neuroprotective, and antinociceptive effects, PEA has the potential as a possible therapy to treat clinical features of patients with COVID-19. Evidence from future clinical trials are welcomed to confirm PEA's beneficial activities and turn this into an effective nutraceutical against the persistent inflammatory status in patients with COVID-19.

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