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COVID-19, Oxidative Stress, and Neuroinflammation in the Depression Route

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Abstract

COVID-19 is associated with oxidative stress, peripheral hyper inflammation, and neuroinflammation, especially in individuals with a more severe form of the disease. Some studies provide evidence on the onset or exacerbation of major depressive disorder (MDD), among other psychiatric disorders due to COVID-19. Oxidative stress and neuroinflammation are associated conditions, especially in the more severe form of MDD and in refractoriness to available therapeutic strategies. Inflammatory cytokines in the COVID-19 hyper inflammation process can activate the hypothalamic–pituitary–adrenal (HPA) axis and the indoleamine-2,3-dioxygenase (IDO) enzyme. IDO activation can reduce tryptophan and increase toxic metabolites of the kynurenine pathway, which increases glial activation, neuroinflammation, toxicity, and neuronal death. This review surveyed a number of studies and analyzed the mechanisms of oxidative stress, inflammation, and neuroinflammation involved in COVID-19 and depression. Finally, the importance of more protocols that can help elucidate the interaction between these mechanisms underlying COVID-19 and MDD and the possible therapeutic strategies involved in the interaction of these mechanisms are highlighted.

Keywords COVID-19 · Oxidative stress · Neuroinflammation · Glial activation · Major depressive disorder

Introduction

In December 2019, the Coronavirus Disease 2019 (COVID-19), resulting from infection by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), made its first appearance in the city of Wuhan, province of Hubei, China, when there were 41 confirmed cases of unknown etiology pneumonia (Zhu et al. 2020; Lu et al. 2020). Later, this new coronavirus, SARS-CoV-2, was identified as a single-stranded RNA virus belonging to group 2B of the β-coronavirus family (Hui et al. 2020).

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Coronaviruses are a large family of viruses that commonly cause changes in the upper respiratory tract and can less often instigate gastrointestinal and neurological disorders in a wide variety of mammals and birds. These viruses have high mutation and recombination rates and propensity to transmission between different species (Zhu et al. 2020). Two coronaviruses have been transmitted from animals to humans, which induce respiratory disease and death in affected individuals. In 2002 and 2003, SARS-CoV was the cause of severe acute respiratory syndrome outbreaks in the province of Guangdong, China (Zhong et al. 2003; Li et al. 2020; Liu et al. 2020). In 2012, the Middle East respiratory syndrome coronavirus (MERS-CoV) was identified as responsible for outbreaks of severe respiratory diseases in the Middle East (Zaki et al. 2012; Muraduzzaman et al. 2018).

MERS-CoV uses dipeptidyl peptidase 4 (DPP4), while SARS-CoV and SARS-CoV-2 depend on angiotensin-converting enzyme 2 (ACE2) to enter the host cell. SARS-CoV-2 expresses the spike protein (S) associated with greater transmissibility due to its multiple mutations. This protein binds to ACE2, activated by transmembrane protease serine

2 (TMPRSS2), thus allowing virus entry to the cell (Ecdc 2020; Ziegler et al. 2020; Deming and Chen 2020). These ACE receptors are expressed in the olfactory mucosa, lung, neuronal, and glial cells in the human CNS (Netland et al. 2008; Lukassen et al. 2020; Brann et al. 2020; Tremblay et al. 2020). In mice, ACE2 can also be observed in the main brain regions involved in blood pressure regulation and body fluid homeostasis, such as in circumventricular organs (CVOs), in the subfornical organ, in the paraventricular nucleus (PVN), in the nucleus of the solitary tract (*nucleus tractus solitarii*, NTS) and in the rostral ventrolateral medulla (Xia and Lazartigues 2010; Nampoothiri et al. 2020). However, despite being highly vascularized, all these regions have little protection from the blood–brain barrier (BBB) (Duvernoy and Risold 2007; Maolood and Meister 2009; Miyata 2015; Bentivoglio et al. 2018). This lack of protection makes these sites vulnerable to circulating pathogens and can be gateways to the brain (Sisó et al. 2010; Bentivoglio et al. 2018). In addition, in an Alzheimer brain, blood–brain barrier fragility is responsible for peripheral inflammation spreading to the brain, leading to cognitive and non-cognitive symptoms (Takeda et al. 2014).

Individuals with COVID-19 usually report changes in the perception of taste and smell, suggesting that SARS-CoV-2 can also affect cells within the central nervous system (CNS) (Dempsey 2021). In addition, histopathological examination of the brains of deceased patients with COVID-19 indicates its potential for CNS invasion (Solomon et al. 2020). This invasion can occur through the neural-mucosal interface by transmucosal entry via regional nervous structures, exploring structures close to the olfactory mucosa, endothelial and nervous tissue, including delicate olfactory and sensory nerve endings. Furthermore, taste buds and gustatory cells in humans do not present ACE2, turning the direct infection and inflammation unlikely to be the reason for taste loss. In this regard, the likely via of cell damage is stratified squamous epithelial cells and filiform papillae, which present ACE2, being infected and progressing to its vicinity causing gustatory cell infection, inflammation, and damage, leading to gustatory system malfunction (Wang et al. 2020). From this, transport can occur along the olfactory tract of the CNS, generating these changes in the perception of smell and taste (Meinhardt et al. 2021). In this way, it was possible to identify viral particles of SARS-COV-2 in the olfactory nerve, in the straight gyrus, and in the brainstem with signs of profound damage to all tissue elements, including glial cells, neurons, their axons, and myelin in a post-mortem analysis of nervous tissue from a person affected by COVID-19-associated severe respiratory failure (Bulfamante et al. 2020).

Thus, SARS-COV-2 can invade the body through various pathways, thus causing systemic and tissue inflammation. This systemic infection presents a massive increase in pro-inflammatory factors in the circulating blood, described as a cytokine storm (Coperchini et al. 2020). Thus, the virus can cross the BBB, considering that inflammatory cytokines induce its instability (Daniels et al. 2014). Alternatively, as already mentioned, the virus can pass through the circumventricular organs or retrograde axonal transport via the olfactory bulb and ultimately infect the brain (Duvernoy and Risold 2007; Sisó et al. 2010; Dempsey 2021).

In addition to the BBB, astrocytes produce another defense mechanism in the brain, reactive astrogliosis, and respond to stimuli, triggering up-regulation of the glial fibrillary acidic protein (GFAP) and with astroglial hypertrophy. Astrogliosis is activated in the face of injury, promoting changes in gene expression, biochemistry, morphology, and physiology, of an inflammatory nature, in astrocytes to protect the CNS against this pathological lesion (Verkhratsky et al. 2017).

Thus, neuroinvasion by SARS-CoV-2 is possible, providing activation of reactive astrogliosis, triggering increased production and secretion of cytokines and other pro-inflammatory factors, and perpetuating neuroinflammation (Daniels et al. 2017; Matschke et al. 2020). As a result, the combination of systemic inflammation, hypoxia resulting from respiratory failure, and neuroinflammation can trigger or exacerbate psychiatric illness (Taylor et al. 2016; Steardo et al. 2020). Thus, like other viral respiratory infections, SARS-CoV-2 can have multiple neurological and psychiatric consequences (Paniz-Mondolfi et al. 2020).

The COVID-19 pandemic has been correlated with depression and anxiety (Huang and Zhao 2020) and it has been hypothesized that some mental disorders will be prevalent in patients that survive after COVID-19 (DePierro et al. 2020). In a survey involving more than 3,900 individuals that had already gone through the COVID-19 disease, conducted between May 2020 and January 2021, 52.4% presented the symptoms that could characterize major depressive disorder (MDD). These results warn about the importance of investigating the potential neuropsychiatric outcomes due to SARS-CoV-2 infection (Perlis et al. 2021). Some patterns can be perceived, such as prevalence in younger respondents, in men, in patients with more considerable COVID-19 severity, and in those who had headaches during acute infection (Perlis et al. 2021). Moreover, a number of researchers evidenced that smell and taste loss due to SARS-COV-2 infection is associated with greater depressive and anxious symptoms (Speth et al. 2020).

This work is a narrative review. Original articles were searched in scientific literature databases, which published relevant evidence on the involvement of oxidative stress and neuroinflammation in SARS-CoV-2 infection and the potential of this condition for triggering the TDM. In addition to the original works, the authors considered literature reviews to observe the discussions and suggestions in the context of

the evolution of the disease's sequelae and as a way of considering studies not found in the database search strategies.

At least two authors read the cited references. This strategy aimed to confirm the relevance of each study and extract some critical data unnoticed by an author.

COVID-19 and Oxidative Stress

Oxidative stress is defined as the imbalance between free radicals and neutralizing molecules. It has as protagonists the oxidizing system, consisting of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which are neutralized by the antioxidant system (Camini et al. 2017). Under physiological conditions, these molecules act on cell signaling, regulating cytokines and growth factors as immunomodulators (Camini et al. 2017) and in the natural aging process (Liguori et al. 2018). However, a high level of these molecules is found in chronic pathologies and viral infections.

Diseases such as diabetes mellitus, cancer, hypertension, and coronary heart disease, among others, have their severity associated with oxidative stress (Yaribeygi et al. 2020). Furthermore, the SARS-CoV-2 family has been noticed in infections, particularly by RNA viruses (Zhang et al. 2019). COVID-19 seems to have exacerbation of the production of free radicals and a reduction in the antioxidants' action. Thus, high levels of oxidative markers in patients with COVID-19 are noticed, and oxidative stress may signal the severity of this and other diseases (Ivanov et al. 2016). Thus, the virus can directly act on brain infection, and the release of inflammatory and/or oxidative markers can cause neuroinflammation and tissue damage.

Reactive species, both oxygen (ROS) and nitrogen (RNS), have unpaired valence electrons (Ivanov et al. 2016; Bensakhria 2018), turning them into highly unstable molecules that can reach adjacent cells. The ROS consist of hydroxyl radical (OH), superoxide anion (O2-), singlet oxygen (O_2), oxygen peroxide (H_2O_2), and ozone (O_3) (Bensakhria 2018). For the RNS, the components are nitric oxide (NO), peroxynitrite (ONOO-), nitrosyl cation (NO+), nitrosyl anion (NO-), and nitrous acid (NH_2O_2) (Camini et al. 2017; Bensakhria 2018). These free radicals are by-products of natural cellular processes and of the functioning of organelles such as mitochondria and the endoplasmic reticulum (Zhang et al. 2019).

Under physiological conditions, homeostasis occurs between release of these molecules and their neutralization by antioxidants. However, with the imbalance, the free radicals have access to different cells, causing deleterious effects on all biomolecules (Ivanov et al. 2016; Bensakhria 2018). Thus, the most reactive hydroxyl radical is able to oxidize molecules such as DNA, phospholipids, and proteins, while the superoxide can generate other free radicals, as well as associate with nitric oxide (NO), and form the peroxynitrite radical (ONOO-), a powerful NO depleted oxidant. When converted to hydroxyl, hydrogen peroxide is able to cross membranes, and ozone is a powerful oxidant of lipid chains, as well as it is able to interact with different organic and inorganic substances, in addition to generating other free radicals (Bensakhria 2018).

The damage caused by free radicals is capable of providing feedback to the system and triggering an oxidative storm, affecting the body as a whole. In this scenario, cell membranes are affected by the phenomenon of lipid peroxidation, protein oxidation, and denaturation. DNA damage occurs and can induce inflammatory immune responses, mutations and tumorigenesis risk, as well as induce cells to apoptosis (Zhang et al. 2019). Thus, oxidative stress is present in autoimmune, neurodegenerative, and chronic renal and cardiovascular diseases, in addition to RNA virus infections (Bensakhria 2018; Liguori et al. 2018; Yaribeygi et al. 2020).

The COVID-19 infection recruits macrophages, which produce high rates of inflammatory molecules and NO. In pro-inflammatory situations, this is a self-reinforcing cycle that contributes to oxidative and nitrosative stress, generating an inflammatory state (Alamdari et al. 2020). High levels of free radicals, along with low levels of antioxidants, cause oxidative stress, worsening the COVID-19 patients' condition (Muhammad et al. 2021). A study of 25 patients with COVID-19 pneumonia and 25 control volunteers found increased levels of nitrite, nitrate, methemoglobin, and oxidative stress in patients with COVID-19. These studies also evidenced that antioxidant substances such as methylene blue, vitamin C, and N-Acetyl cysteine induced therapeutic responses, improving the survival rate of critically ill patients (Alamdari et al. 2020).

Patients with a COVID-19 diagnosis in an intensive care unit presented low levels of vitamin C, thiol protein, glutathione, γ-tocopherol, and β-carotene in peripheral blood. Increased copper was also observed when compared to zinc in 55% of the patients. Increased copper has been linked to lipid peroxides. Furthermore, there was an increase in the levels of C-reactive protein and myeloperoxidase. In summary, there was an increase in lipid peroxidation and deficits in some antioxidants (Pincemail et al. 2021). A cross-sectional study of 50 patients diagnosed with COVID-19 conducted in Jigawa, northwestern Nigeria, found low levels of vitamins A, C, and E, glutathione, glutathione peroxidase, catalase, and superoxide dismutase. In addition, the researchers observed low levels of selenium, zinc, magnesium, chromium, and malondialdehyde and high rates of oxidative stress marker 8-isoprostaglandin F2 alpha in the blood of the patients, when compared to the controls (Muhammad et al. 2021).

Based on the scientific literature, it is possible to infer that oxidative stress is a hallmark among the pathophysiological mechanisms of COVID-19.

COVID-19 and Neuroinflammation

Inflammation is a response present in evolved organisms, fighting against detrimental stimuli such as tissue damage and microbial infection. Acute inflammation is thought to be the first-line defense, and it is a component of the innate immune system (Ahmed 2011; Zhou et al. 2020a; Arunachalam et al. 2020; Hoagland et al. 2021).

SARS-CoV-2 exerts detrimental effects on neurological functions assessing this complex system through multiple pathways such as the neuronal pathway, blood circulation, and direct infection (Fig. 1) (Wu et al. 2020). The most important ones in this regard are the first and second pathways. In the neuronal pathway, the viruses infect motor or sensory nerve endings, activating neuronal transport mechanisms, which frequently occur in the olfactory fibers due to their singular organization that connects the nasal cavity directly to the central nervous system (CNS) (Koyuncu et al. 2013; Swanson and McGavern 2015). In the bloodstream, it is proposed that the virus can reach the CNS by binding to the ACE2 receptor in the blood–brain barrier (BBB) or by entering in monocytes and macrophages to freely cross the BBB (Zhou et al. 2020b). In addition, although macrophages work as a defense mechanism in a great range of infections, including virus infections, in SARS-CoV-2 infection it enables viral adhesion and anchoring to pulmonary parenquima and allows the virus to enter the organism through ACE2, as well as to replicate in their interior (Uversky et al. 2021).

It is known that SARS-CoV-2 induces pro-inflammatory cytokines up-regulation, leading to a cytokine storm (Barnes et al. 2020). Among the pro-inflammatory cytokines induced in SARS-CoV-2 infection, tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), IL-1β, interferon-γ (IFNγ), monocyte chemoattractant protein 1 (MCP1), and

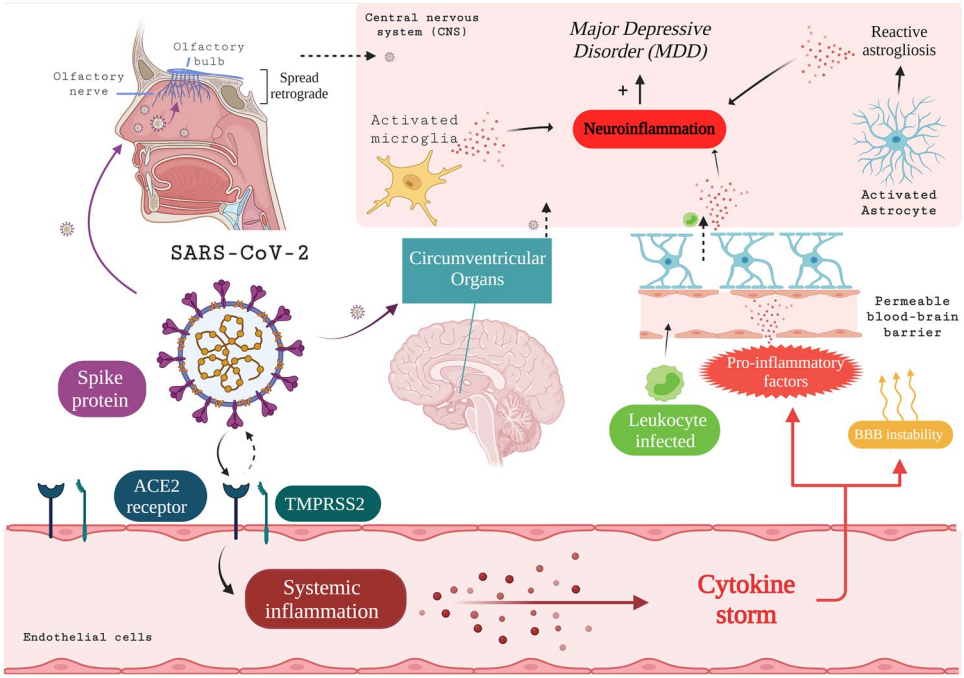

Fig. 1 Invasion pathways of SARS-CoV-2, neuroinflammation, and MDD. SARS-CoV-2 can invade the body through various pathways, thus causing systemic inflammation. The virus uses enzyme ACE2 as an entry receptor for cell invasion, resorting to TMPRSS2 to initiate its S protein of ACE2. The ACE2 expression is known in human blood vessel endothelial and microvasculature cells. Thus, invasion by the virus causes systemic inflammation, whose main characteristic is the activation of the cytokine production cascade, called cytokine storm. This systemic inflammation compromises permeability of the blood–brain barrier (BBB), making it unstable. With this, the brain is flooded with pro-inflammatory factors, and the passage is free for SARS-CoV-2 neuroinvasion, which can be through infected leukocytes. This process will activate microglia and astrocytes, which will release more pro-inflammatory factors. From this, neuroinflammation propagates, which is positively associated with MDD. The virus can also reach the CNS through the circumventricular organs, midline structures around the third and fourth ventricles, which the BBB does not protect. Another gateway is through the olfactory epithelium, in which the virus propagates through the olfactory nerve, crossing the cribriform lamina and reaching the olfactory bulb in the CNS. This way is retrograde dissemination, through trans-synaptic transfer, using endocytosis and exocytosis processes of vesicles containing the virus, with subsequent axonal transport to the neuronal cell bodies. The images were extracted from the BioRender app

granulocyte–macrophage colony-stimulating factor (GM-CSF) stand out (Beltrán-García et al. 2020). The innate immune cells are activated in COVID-19, and the mast cells play an important role in this regard, releasing histamine, cytokines, and chemokines, raising the inflammatory reactions, which makes mast activation a major contributor to neuroinflammation and neurodegeneration (Kempuraj et al. 2016, 2017, 2020). Furthermore, coagulation disorders, present in COVID-19 patients, increase neuroinflammation, stroke, and cognitive decline risks (Pezzini and Padovani 2020). In addition, glial cells play a major role in neuroinflammation. In physiological conditions, the glia is able to modulate neuronal environment leading to homeostasis, and, in pathological conditions, it can induce neuroinflammation. The microglia function as resident macrophages in the CNS depending on the phagocytic activity, mediated by triggering receptor expressed on myeloid cells 2 (TREM2) (Gogoleva et al. 2019). Therefore, after SARS-CoV-2 infection, the immune system is up-regulated, promoting many different molecules that can act in the CNS by different pathways. The presence of a virus in the CNS associated with the pro-inflammatory response leads to inflammation in the neuronal tissue, which is thought to be one of the relevant mechanisms causing neural alterations in COVID-19 patients (Kempuraj et al. 2020).

Some people present cognitive impairment after being diagnosed with COVID-19. One hypothesis for this change is related to neuroinflammation markers and to microvascular lesions involved in Alzheimer's disease. In addition, patients diagnosed with COVID-19 may have biomarkers of Alzheimer's disease in blood and cerebrospinal fluid (Zhou et al. 2021).

Peripheral infection can inflame BBB cells, such as those in the choroid plexus, thus transmitting inflammation to the brain parenchyma. In this study, the authors observed increased microglial activation genes associated with COVID-19 and suggested that activated microglia emerge from increased inflammation in the CNS. Microglial subgroups in the cerebral cortex after COVID-19 death were also evidenced. These characteristics are associated with neurodegenerative diseases. Thus, this study suggests that acute viral infection can cause lasting neuroinflammation, predisposing individuals to neurodegeneration and neuropsychiatric diseases (Yang et al. 2021).

In a cohort study, researchers evidenced seven variants of the gene for IL-6 and five variants of the IL-6 receptor (IL-6R) in the peripheral blood of a general population, which appear to be involved in neurodegenerative diseases and in COVID-19 severity, with neuroinflammation as a frequent cause. The authors suggest extensive investigation of the pleiotropic function of IL-6 as a therapeutic target for severe cases or with the possibility of increased COVID-19 severity and implications for the CNS (Strafella et al. 2020).

COVID-19, Oxidative Stress, and Neuroinflammation

Severe cases of COVID-19 have shown hyper inflammation caused by a cytokine storm (Mehta et al. 2020). However, new analyses have led to a possible oxidative storm due to high lipid peroxidation and oxidation of membrane proteins. These deleterious effects can contribute to a transformation and hyalinization of the pulmonary alveolar membranes (Xu et al. 2020), accelerating the process of tissue stiffness and causing lethal respiratory distress. Thus, the risk factor for groups such as older adults and people with diabetes, hypertension, and cardiovascular diseases is understood, as these individuals already have a state of oxidative stress (Liguori et al. 2018; Yaribeygi et al. 2020).

A chronic low level of oxidative stress and inflammation, added to the changes caused by a viral infection, seems to be responsible for the most severe forms of COVID-19 (Zhou et al. 2020a, b, c), as they cause viruses to induce high production of free radicals and depletion of antioxidants (Camini et al. 2017). The increase in ROS may occur due to a mitochondrial dysfunction caused by penetration of the virus into the cell or by signaling exacerbated by the "cytokine storm" with release of Il-2, Il-6, Il-7, and TNF-α (Mehta et al. 2020). Similarly, immune cells such as macrophages and neutrophils play a potential pathological role (Merad and Martin 2020) by producing and secreting high pro-inflammatory cytokines and ROS levels. This uncontrolled production increases oxidative stress, and hyper inflammation can affect the immune system, altering immune cell function and the inflammatory response (Galley 2011; Nagar et al. 2018).

A number of studies indicate the role of angiotensin II (Ang II) in the activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (Dikalov and Nazarewicz 2013; Rincón et al. 2015) by binding to the angiotensin I receptor (AT1R) (Valente et al. 2012) and, thus, in ROS release. Angiotensin-converting enzyme-2 (ACE2) participates in the binding of the virus to the human cell and allows viral entry into the cell membrane. Thus, with a SARS-CoV-2 infection, there is a reduction in the ACE2 bioavailability and an increase in the interaction between angiotensin and the production of free radicals. The entry of the virus itself and the viral load can modulate oxidative stress and the inflammatory response, both processes that directly contribute to COVID-19 severity (Fig. 2) (OUDIT et al. 2007; Sawalha et al. 2020).

Hyper inflammation is triggered by the cytokines and can be accompanied by cytopenia and hyperferritinemia (Camini et al. 2017; Bensakhria 2018). ROS production occurs by Fenton reaction $(Fe(II) + H2O2 \rightarrow Fe(III) + H$

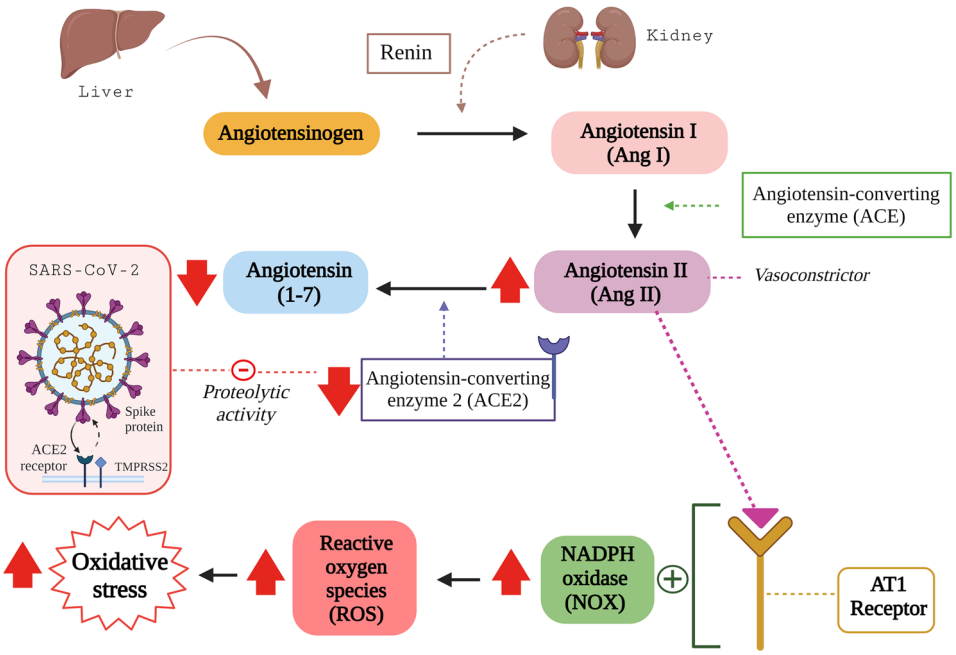

Fig. 2 SARS-CoV-2, ACE2 and oxidative stress. SARS-CoV-2 can modulate oxidative stress and the inflammatory response, both processes that directly contribute to COVID-19 severity. Coming from the liver, angiotensinogen is cleaved by renin, and released by the kidneys to angiotensin I (Ang I), which is then converted to angiotensin II (Ang II) through the action of ACE. Ang II is a potent vasoconstrictor, which uses the AT1 receptor to signal the NF-κB transcription factor, which results in the activation of NADPH oxidase (NOX), an essential source of ROS production. Ang II will be converted to angiotensin (1–7) through ACE2. However, SARS-CoV-2 uses ACE2 for cell invasion, promoting a decrease in the expression of this enzyme and suppressing its proteolytic activity. With this enzyme's local or systemic depletion, there is an increase in the level of Ang II and, consequently, a more significant induction of ROS production via NOX in endothelial cells, triggering mitochondrial oxidative stress and endothelial dysfunction. The images were extracted from the BioRender app

$O^{-} + HO^{-}$) (Ivanov et al. 2016). This mechanism occurs through the attack of SARS-CoV-2 on the hemoglobin (Hb) groups of red blood cells, concentrating Fe(III) ions in the bloodstream (Chen et al. 2020) which in turn produces an increase in the ferritin levels (Zhou et al. 2020a, b, c). Thus, hemoglobinopathy and iron dysmetabolism caused by the infection culminates in oxidative stress, ferroptosis, lipid peroxidation, and mitochondrial damage, among others (Cavezzi et al. 2020).

Cytokines stimulate nitric oxide synthase (NOs) isoforms and, consequently, the production of nitric oxide (NO), which can react with the superoxide ion and generate the potent oxidizing peroxynitrite radical (ONOO-) (Camini et al. 2017). In this scenario, as juveniles are exposed to physical, chemical, and biological factors, tissue ischemia may neutralize the cofactors of antioxidant enzymes, such as superoxide dismutase and NADPH oxidase myeloperoxidase, preventing return to the body homeostasis (Camini et al. 2017; Bensakhria 2018).

COVID-19 and the Hypothalamus Pituitary Adrenal (HPA) Axis

The HPA axis is a neuroendocrine component that integrates the hypothalamus, pituitary, and adrenal glands, working through a complex positive and negative feedback system depending on hormones and receptors in these three organs, modulating multiple physiological and pathological processes. The HPA axis function starts at the hypothalamus that releases the corticotropin-releasing hormone (CRH) that will up-regulate the pituitary gland to produce adrenocorticotropic hormone (ACTH), releasing it into the bloodstream. ACTH will induce the adrenal gland to synthesize glucocorticoids as cortisol (DeMorrow 2018).

COVID-19 is considered a systemic disease, as it affects organs in the entire body (Guan et al. 2020; Gavriatopoulou et al. 2020). The ACE2 enzyme is expressed in many places, such as venous and arterial endothelial cells, which irrigate

and drain the adrenal glands (Pal 2020). Some studies have observed that ACE2 is related to a reduction in the HPA axis activity and that it is involved in beneficial effects on stress-related behavioral changes (Wang et al. 2018).

Severe acute respiratory syndrome (SARS-CoV), considered remarkably similar to SARS-CoV-2, is one of the primary immune invasive strategies to deregulate the cortisol response to the antigen. It does so through the expression of amino acid sequences that mimetize parts of the ACTH sequence. Therefore, immune system strategies to fight against the infection would accidentally destroy ACTH, consequently causing an alteration in the cortisol dynamics in COVID-19 patients (Pal 2020).

SARS viruses are linked with hypothalamus and pituitary gland alterations. There is evidence that 40% of the 63 patients that went through SARS infection had central adrenal insufficiency for some time. The presence of hypothyroidism and low rates of dehydroepiandrosterone sulfate suggests hypothalamus-pituitary damage (Leow et al. 2005; Al-Aridi et al. 2011; Mocking et al. 2015; Zhu et al. 2015; Alzahrani et al. 2021). There are two main hypotheses by which the hypothalamus-pituitary axis could interact with ACE2: the first one is through blood, and the cribriform plate directs the second one. In that regard, autopsy studies have shown SARS-CoV samples and neuronal degeneration in the hypothalamus (Pal 2020).

It is important to mention that COVID-19 patients with more severe diseases had reduced ACTH and cortisol rates (Alzahrani et al. 2021). Despite the similarity between SARS-CoV-2 and SARS-CoV, more studies about the clinical manifestations in HPA caused by the virus responsible for the COVID-19 pandemic are necessary.

COVID-19, Oxidative Stress, Neuroinflammation, and MDD

An online survey noted an increase in some psychiatric disorders due to the pandemic and an even more significant increase in suicidal ideation in people who had experienced COVID-19 and presented positive screening for MDD and generalized anxiety disorder (Tsai et al. 2021). The patients diagnosed with COVID-19 who required hospitalization, were assessed using questionnaires about post-traumatic stress disorder, depression, anxiety, trauma exposure, resilience, and perceived social support. A total of 898 patients were evaluated, of which 13.2% had post-traumatic stress disorder, 21.0% suffered from depression, and 16.4% presented MDD (Chen et al. 2021).

Major depressive disorder (MDD) has a multifactorial etiology and is related to high oxidative stress and neuroinflammation levels. MDD severity can be associated with high levels of circulating cytokines (Reichenberg et al. 2001; Harrison et al. 2009; Grigoleit et al. 2011; Köhler et al. 2017; Kageyama et al. 2018; Zou et al. 2018). Early life stress and chronic stress in adult life are highly contributing situations to the deterioration of the patient's clinical condition. The MDD pathophysiology and periods of chronic stress involve an exacerbated and uncontrolled increase in the body's immune response, causing increased inflammatory cytokines, such as TNF-α, IL-1β, IL-6, and IL-12. Presence of these cytokines in high levels was associated with increased numbers of non-classical monocytes (Ellul et al. 2016; Kim and Won 2017; Ignácio et al. 2017; Nowak et al. 2019; Peng et al. 2021; Gumpp et al. 2021; Tuon et al. 2021). Both oxidative stress and neuroinflammation cause damage to brain tissue (Ignácio et al. 2017).

The kynurenine pathway is linked to inflammation in MDD through the action of kynurenines, metabolites of the kynurenine pathway that present neurotoxicity when released in an exacerbated manner, in addition to reducing serotonin synthesis. This neurotransmitter has reduced levels in cases of MDD. Some metabolites of the kynurenine pathway have pro-inflammatory functions, such as quinolinic acid (QA), 3-hydroxykynurenine (3-HK), and 3-hydroxy-anthranilic acid (3-HAA) (Kubacka et al. 2020; Tuka et al. 2021). With the prolonged release of pro-inflammatory cytokines, there is inhibition of the function of glucocorticoid receptors in the hippocampus and an increase in reactive oxygen species, generating a vicious cycle highly linked to MDD and COVID-19 (Kim et al. 2016; Di Nicola et al. 2020). In this sense, some studies suggest that the cytokine storm that is present, especially in more severe COVID-19 patients, may activate the indoleamine 2,3-dioxygenase 1 (IDO-1) enzyme and, consequently, culminate in a drastic reduction of tryptophan, increases in toxic metabolites of the kynurenine pathway, and depression (Bouças et al. 2020).

COVID-19 can trigger a storm of cytokines that involve the same substances present in neuroinflammation in cases of MDD, such as IL-6, IL-1β, and TNF-α. In addition, infection by SARS-CoV-2 stimulates the innate immune system to release mast cells, monocytes, dendritic cells, and T cells, among others (Kempuraj et al. 2020). SARS-CoV-2 has been shown to exert an action of exacerbating depressive symptoms or even stimulating development of the disorder (Grolli et al. 2021).

A prospective, observational, and cross-sectional clinical study conducted between April and August 2020 with one hundred and twenty-seven patients separated the volunteers into three categories, which were patients diagnosed with mild, moderate, or severe forms of COVID-19. The patients with the severe form of the disease had higher rates of superoxide anion radicals and lower rates of nitric oxide when compared to the other groups. Furthermore, catalase was increased in the moderate group when

compared to the group that presented the severe form of the disease (Cekerevac et al. 2021).

COVID-19, Neuroinflammation, and Glial Activation in MDD

SARS-CoV presents angiotensin-converting enzyme 2 (ACE2) as its functional cell invasion receptor (Li et al. 2003). Through its spike protein (S) and transmembrane serine protease 2 (TMPRSS2) action, a serine protease, SARS-CoV-2 couples to the ACE2 receptor to promote its entry into cells (Hoffmann et al. 2020; Zhou et al. 2021). Given the presence of ACE2 receptors in microglia and astrocytes, it may be possible to relate SARS-CoV-2 with glial activation (Tremblay et al. 2020). In fact, some studies have shown microglial and astrocytic activation in the CNS of COVID-19 patients who had more severe conditions and encephalopathies (Pilotto and Padovani 2020; Matschke et al. 2020; Meinhardt et al. 2021). On the other hand, the virus seems to predominantly infect immune and vascular cells, thus causing a local inflammation that up-regulates astrocytes and microglia, potentiating the effects of circulating systemic cytokines in the severe form of the disease (Solomon et al. 2020). An in vitro research study evaluated the Spike protein, a product of the SARS-CoV-2 virus that releases exosomes with microRNAs. These mRNAs are internalized by microglia and hyperactivate the expression of genes related to the expression of pro-inflammatory substances, such as TNFa, NF-kB, and IFN-b, triggering neuroinflammation (Mishra and Banerjea 2020).

In addition to this direct activation, human coronaviruses infect peripheral myeloid cells, which can be recruited to transmigrate to the CNS under conditions of inflammation or psychological stress in situations where there is an increase in the permeability of the BBB. In the CNS, neuroinflammation is propagated through infected monocytes, which promote the release of pro-inflammatory cytokines, such as IL-6, IL-8, IL-10, IL-2R, and TNF-α, and stimulation of microglia, contributing to neuropsychiatric symptoms resulting from COVID-19 (Fig. 3) (Wohleb et al. 2015; Hong and Banks 2015; Desforges et al. 2019; Troyer et al. 2020).

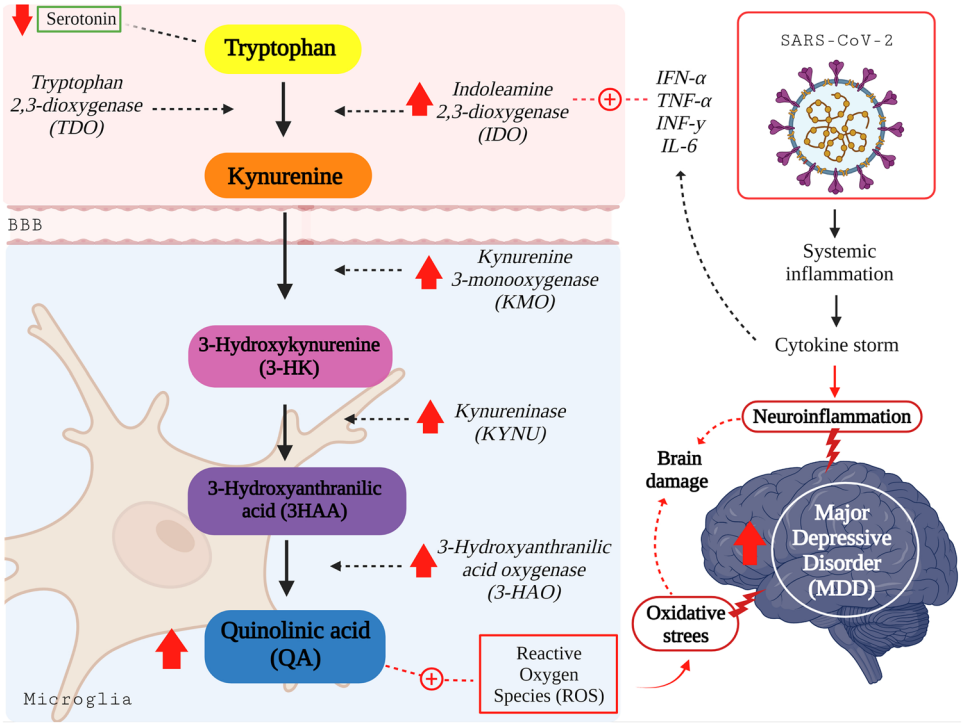

Fig. 3 COVID-19 and glial activation by the kynurenine pathway — MDD route. SARS-CoV-2 induces a cytokine storm. Pro-inflammatory cytokines such as INF-α, TNF-α, IFN-y, and IL-6 stimulate the action of IDO, which, together with TDO, is responsible for converting tryptophan into kynurenine. Proportionally, with the increased action of IDO, there is an increase in the conversion of available tryptophan into kynurenine. With that, there is greater kynurenine pathway activity and lower tryptophan bioavailability for the serotonin pathway. Another action of pro-inflammatory cytokines is to increase the action of enzymes in the QA transformation chain in the microglia. KMO, KYNU, and 3-HAO have their activities increased, thus promoting greater conversion of KYN into its end product: QA. This neurotoxic metabolite can positively affect ROS production, promoting oxidative stress. Neuroinflammation and oxidative stress result in brain damage and in major depressive disorder (MDD). The images were extracted from the BioRender app

In a postmortem study with patients who died due to COVID-19, the researchers evidenced infiltration of cytotoxic T lymphocytes and astrogliosis in the brain tissues, being more pronounced in the brainstem and cerebellum (Matschke et al. 2020). Other postmortem surveys of three COVID-19 patients with severe symptoms showed that the cerebral cortex had increased numbers of reactive astrocytes and exacerbated microglial activation, as well as decreased glutathione levels and up-regulation of genes related to IL-1B, IL-6, interferon-inducible transmembrane, MX dynamin-like GTPase 1, and 2′,5′-oligoadenylate synthetase 2, suggesting a relationship between oxidative stress and neuroinflammation mediated by glia (Boroujeni et al. 2021). Another research study observed that microglial activation in the postmortem brainstem was exacerbated. In addition, there was an increase in innate immunity with microglial activation (Poloni et al. 2021). Plasma concentration of the astrogliosis marker, GFAP, was also increased in patients with moderate to severe COVID-19 (Kanberg et al. 2020).

Glial cells are critical regulators of CNS homeostasis under physiological conditions. These cells also express indoleamine 2,3-dioxygenase (IDO). IDO is positively stimulated by cytokines and is closely related to the kynurenine pathway, already associated with the development of MDD. Briefly, IDO, originating from brain cells and from the immune system, together with tryptophan 2,3-dioxygenase (TDO), from the liver, is responsible for converting tryptophan, an essential amino acid precursor of serotonin, into kynurenine. With the presence of pro-inflammatory cytokines, such as IFN-α, TNF-α, INF-y, and IL-6, there is super stimulation of the action of IDO, which promotes an increase in the conversion of available tryptophan into kynurenine, thus causing greater activity of the kynurenine pathway and lower tryptophan bioavailability for the serotonin synthesis pathway (Raison et al. 2010; Ogawa et al. 2014; Anderson et al. 2016; Dell'Osso et al. 2016; Doolin et al. 2018).

Changes in tryptophan metabolism within the kynurenine pathway were correlated with increased IL-6 in COVID-19 patients (Thomas et al. 2020). Other researchers provide evidence for an increased rate of kynurenine relative to tryptophan in serum from COVID-19 patients and suggest that these results reflect the increased inflammation level in infected patients (Lionetto et al. 2021).

In the kynurenine pathway, an action of pro-inflammatory cytokines in microglia is to increase the action of the enzymes that participate in the pathway of quinolinic acid (QA), a neurotoxic metabolite. Among the effects of QA are reactive oxygen species (ROS) generation, BBB disruption, cell cytoskeleton destabilization, promotion of tau phosphorylation, impairment in autophagy processes, and MDD (Guillemin et al. 2003; Ganzella et al. 2006; Braidy et al. 2009; La Cruz et al. 2012; Pierozan et al. 2018; da Silveira et al. 2018; Ferreira et al. 2018).

The enzymes associated with the QA chain, kynurenine 3-monooxygenase (KMO), kynureninase (KYNU), and 3-hydroxyanthranilic acid oxygenase (3-HAO) have their activities increased in the microglia due to pro-inflammatory cytokines. Thus, there is greater conversion of kynurenine (KYN) into its final product, QA, increasing the production of this neurotoxic metabolite and, indirectly, decreasing KYN bioavailability for the production of the neuroprotective metabolite, kynurenic acid (KynA) (Heisler and O'Connor 2015). To corroborate, patients who had attempted suicide had increased levels of QA in the cerebrospinal fluid (Steiner et al. 2011; Erhardt et al. 2013; Schwieler et al. 2020).

COVID-19 patients had higher levels of depression, anxiety and post-traumatic stress disorder (PTSD) symptoms when compared to the control group. In this study, it was observed that the levels of peripheral blood C-reactive protein (CRP), the peripheral inflammatory indicator, were positively related to the severity of depression (Guo et al. 2020). Another study tracked psychiatric symptoms in 402 adult individuals diagnosed with COVID-19 for 1 month after hospital treatment. Overall, 56% of these individuals have scored in the pathological range of at least one psychiatric dimension. Of the 402 individuals, 42% fell into the psychopathological range for anxiety, 40% for insomnia, 31% for depression, 28% for PTSD, and 20% for obsessive–compulsive (OC) symptoms. Within these groups, female individuals stood out in the anxiety and depression results. In addition, individuals who already had a previous psychiatric history obtained high scores on most of the psychopathological measures. Another relationship that can be observed was the depression and anxiety scores positively associated with the baseline systemic immune-inflammation index (SII), which is based on peripheral lymphocyte, neutrophil, and platelet counts to reflect the immune response to the systemic inflammation generated (Mazza et al. 2020).

Future Directions and Conclusion

Since the first research study on COVID-19 symptoms and pathophysiology, challenges have been pointed out, considering the possibility of virus entry into the CNS or of neurophysiological changes from peripheral inflammation, among other systemic conditions developed in SARS-CoV-2 infection (Ng Kee Kwong et al. 2020; Kotfis et al. 2020). Considering the conditions imposed on the CNS due to neuroinflammation, even mild in children and adolescents, some authors even argue about possible future damage and neuropsychiatric conditions (Serrano-Castro et al. 2020).

The cytokine storm caused by COVID-19 can damage the BBB, leading to triggering or exacerbation of neuroinflammation, a condition present in MDD, among other psychiatric disorders and various CNS diseases (Kempuraj et al. 2020).

A close association between individuals who were affected by COVID-19 and the presentation of psychiatric signs and symptoms can be considered. This relationship is emerging and still needs many studies, especially considering the number of people affected by the virus during the pandemic and which may result in mental illness. Thus, longitudinal monitoring of patients after COVID-19 should be proposed, paying attention to the neuroimmune status and signs and symptoms of psychiatric disorders. This follow-up should encompass the different moments throughout the life course of individuals exposed to SARS-CoV-2. It will be possible to verify and evaluate the course of the remaining mental and behavioral impacts of COVID-19 on the affected population (Troyer et al. 2020).

It is crucial to highlight post-mortem studies, which observed infiltration of inflammatory markers, increased oxidative stress, and increased astrocytic reactivity, astrogliosis, and microglial activation in the brain tissues of individuals who died after COVID-19-related complications (Kanberg et al. 2020; Boroujeni et al. 2021). Thus, despite the lack of studies relating oxidative stress, neuroinflammation, and depression, diverse evidence suggests that these pathophysiological mechanisms emerge from COVID-19 and are potent intertwined factors, both in MDD induction and exacerbation.

Another important mechanism related to hyper inflammation and glial activation is related to the neurotoxic metabolites of the kynurenine pathway. Greater activation of the kynurenine pathway in COVID-19 has already been shown. The shift of tryptophan metabolism towards the kynurenine pathway is also related to increased oxidative stress and is a relevant mechanism involved in MDD. Thus, the toxic function of kynurenine pathway metabolites from SARS-CoV-2-induced hyper inflammation is another potential mechanism that involves oxidative stress and triggers or exacerbates MDD.

Research on the symptoms and pathophysiological mechanisms involved in COVID-19 provides strong evidence for oxidative stress, hyper inflammation, and brain alterations underlying glial activation and neuroinflammation from COVID-19 in triggering and exacerbating MDD. Based on this evidence, it is possible to point out the importance of studies that can relate the interaction of these mechanisms in survivors of COVID-19 survivors in order to elucidate the involvement of the disease in MDD and provide suggestions on new studies that can advance the discovery of more effective therapies to for MDD.

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Declarations

Ethics Approval and Consent to Participate Not applicable.

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