Chapter

COVID-19: A Catalyst for Novel Psychiatric Paradigms - Part 1

Adonis Sfera, Carolina Osorio, Jose E. Campo Maldonado, Afzaal Jafri, Aaron D. Chokka, Carlos Manuel Zapata Martín del Campo and Zisis Kozlakidis

Abstract

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) emerged in the late 2019 and spread rapidly throughout the world, becoming a pandemic in March 2020. It became obvious early that the prognosis of this illness is highly variable, ranging from few mild symptoms to severe complications and death, indicating that aside from the pathogen virulence, host factors contribute significantly to the overall outcome. Like SARS-CoV and Human Coronavirus NL63 (HCoV-NL63-NL63), SARS-CoV-2 enters host cells via several receptors among which angiotensin converting enzyme-2 (ACE-2) are the most studied. As this protein is widely expressed in the lungs, blood vessels, brain, kidney, testes and ovaries, the effects of this virus are widespread, affecting many body tissues and organs. Viral attachment to ACE-2 downregulates this protein, disrupting angiotensin II (ANG II) hydrolysis that in return contributes to the unchecked accumulation of this peptide. ANG II toxicity is the result of excessive activation of ANG II type 1 receptors (AT-1Rs) and N-methyl-D-aspartate NMDA receptors (NMDARs). Overstimulation of these proteins, along with the loss of angiotensin (1–7) (ANG 1–7), upregulates reactive oxygen species (ROS), inflicting end-organ damage (hit 1). However, a preexistent redox impairment may be necessary for the development of SARS-CoV-2 critical illness (hit 2). Here we propose a two-hit paradigm in which COVID-19 critical illness develops primarily in individuals with preexistent antioxidant dysfunction. Several observational studies are in line with the two hit model as they have associated poor COVID-19 prognosis with the hereditary antioxidant defects. Moreover, the SARS-CoV-2 interactome reveals that viral antigen NSP5 directly inhibits the synthesis of glutathione peroxidase (GPX), an antioxidant enzyme that along with glucose-6-phosphate dehydrogenase (G6PD) protect the body from oxidative damage. Indeed, individuals with G6PD deficiency have less favorable COVID-19 outcomes compared to the general population.

Keywords: Sars-CoV-2, antiviral psychotropic drugs, glucose-6-phosphate dehydrogenase, glutathione peroxidase, endocytic pathway, calmodulin

1. Introduction

The COVID-19 pandemic has altered many aspects of daily life, contributing to the higher incidence of psychiatric conditions, including depression, anxiety,

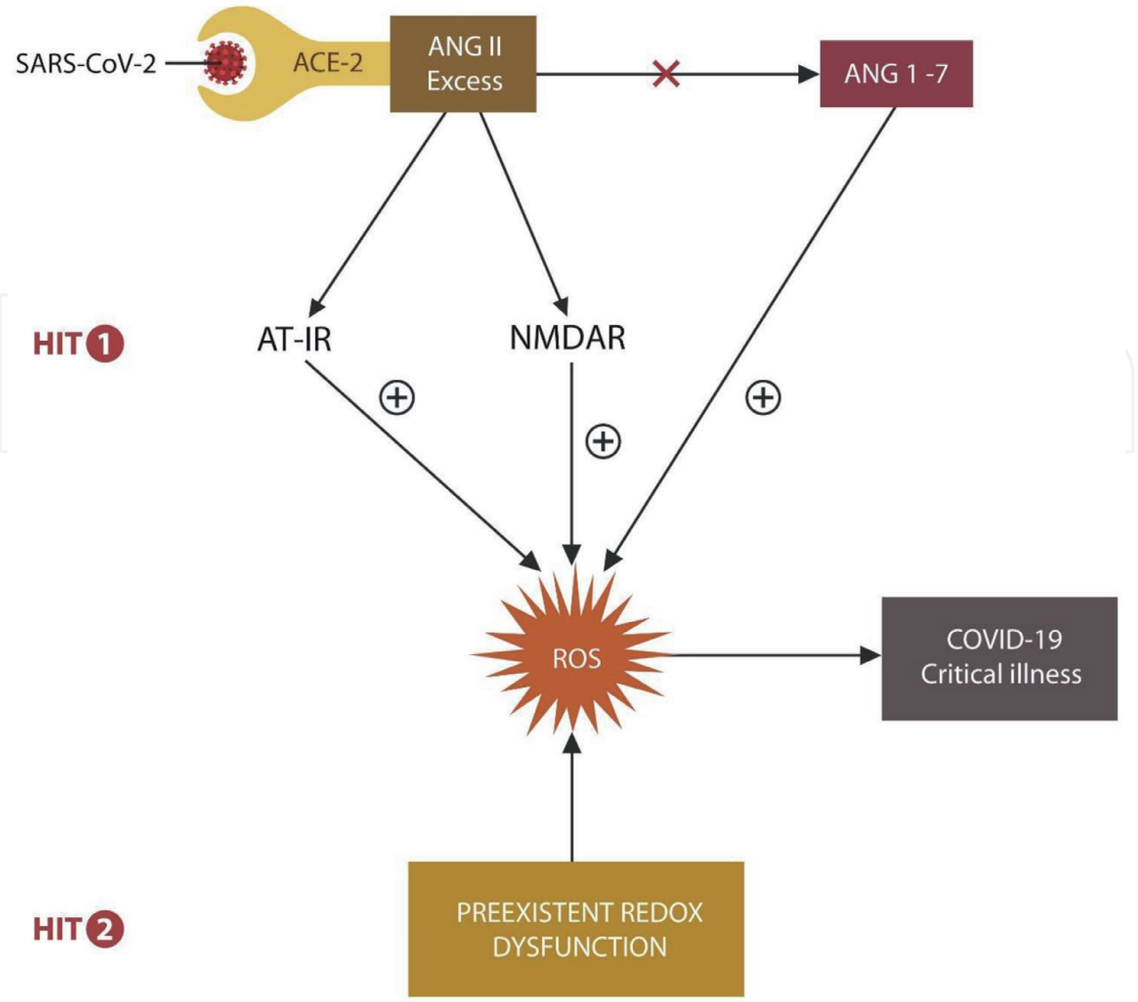

Figure 1.
The two-hit paradigm: Excessive angiotensin II (ANG II) and loss of angiotensin (1–7) (ANG 1–7) generate oxidative stress both directly and indirectly (via ANG II-AT-1R and ANG II-NMDAR axes). COVID-19 critical illness is triggered when a preexistent redox dysfunction (second hit) is present.

posttraumatic stress disorder (PTSD) and substance use [1–8]. In addition, as SARS-CoV-2 is a neurotropic virus, delirium, cognitive impairment and psychosis were demonstrated in up to 40% of infected patients [9–11]. Moreover, like the previous pandemics, COVID-19 may be followed by delayed or even next-generation neuropsychiatric sequelae [12–14]. For example, the offspring of women pregnant during the 1918 influenza pandemic achieved lower education, socioeconomic status, and income as adults, indicating hidden and long-lasting effects [15] (**Figure 1**).

2. COVID-19 and psychotropic drugs

Several psychotropic drugs have been associated with antiviral and antitumor properties, suggesting that they may lower the severity of COVID-19 critical illness [16]. For example, imipramine, clomipramine and the phenothiazine class of drugs have demonstrated efficacy against other viruses, including Ebola, Dengue and West Nile [17–20]. In addition, thioridazine, another phenothiazine, was found to slow the progression of lung cancers, probably by enhancing antitumor immunity [21]. Other antipsychotics evidenced some beneficial

effects in patients with glioblastoma and pancreatic cancer, suggesting immuno-oncological properties [22].

The recently published SARS-CoV-2/host protein–protein interaction and phosphorylation studies demonstrated viral interference with several pathways previously implicated in psychiatric disorders and targeted by psychotropic drugs [23, 24]. For example, upon binding to ACE-2, the SARS-CoV-2 virus ingresses host cells via the endocytic pathway (EP), a vesicular system inhibited by chlorpromazine (CPZ) and linked to schizophrenia and neurodegenerative disorders [25, 26]. Indeed, several antipsychotic drugs were found to interact with both the EP and extracellular vesicles (EVs), demonstrating previously unknown mechanisms of action [27, 28]. Other pathways involved in both the SARS-CoV-2 infection and psychiatric illness include autophagy, redox and calmodulin systems, connecting the virus to neuropathology [23, 29–31].

Several studies have associated NMDARs with sigma-1 nonopioid receptor, a protein hijacked by the SARS-CoV-2 to enable viral entry and replication [24, 32]. Indeed, sigma-1 agonists, such as fluvoxamine, sertraline and the antipsychotic drug, haloperidol inhibit exploitation of sigma-1, dampening viral ingress [33–35]. In addition, fluvoxamine was found to decrease ANG II-induced cardiac hypertrophy, indicating protective effects against both the SARS-CoV-2 infection and its complication [36]. Moreover, ifenprodil, an NMDAR antagonist (and sigma-1 receptor agonist), is currently in phase III clinical trials for COVID-19, linking oxidative stress to the severity of SARS-CoV-2 infection [37] (NCT04382924).

In the immune compartment, both COVID-19 and schizophrenia were associated with dysregulated inflammatory processes and lower levels of regulatory T cells (Tregs), suggesting possible autoimmune pathology [38–40]. In contrast, antipsychotic drugs were found to upregulate Tregs, lowering autoimmune inflammation [39]. Indeed, NMDARs are abundantly expressed not only in the central nervous system (CNS) but also in the immune compartment where they regulate T-cell proliferation in response to antigens. Along these lines, NMDAR antagonists, including antipsychotic drugs upregulate Tregs, enhancing immunological tolerance that in return decreases neuroinflammation [41].

In the following sections, we take a closer look at the SARS-CoV-2 interactome, looking for pathways altered by viral infection, psychiatric disorders and the action mechanism of psychotropic drugs. In other words, learning from the virus to design better psychiatric treatments (**Table 1**).

SARS-CoV-2	Phenothiazines	References
Internalization via EP endocytosis	Inhibit EP endocytosis	[42]
Lowers autophagy	Augment autophagy	[43]
Augments calmodulin	Lower calmodulin	[44]
Augments sigma-1 receptor signaling	Lower sigma-1 receptor signaling	[45]
Lower regulatory T cells (Tregs) number	Upregulate the number of regulatory T cells (Tregs)	[39]

Table 1.
Phenothiazine class of antipsychotic drugs oppose several SARS-CoV-2 actions.

3. The SARS-CoV-2 interactome and viral infection

SARS-CoV-2 is an enveloped, positive-sense, single-stranded, RNA virus with a genome of 30 kb, encoding for 29 viral proteins. These proteins target about 332 human molecules, some of which are also involved in psychiatric disorders and the action mechanism of psychotropic drugs [24]. The virus accesses host cells via its spike (S) glycoprotein that attaches to the cell surface receptor ACE-2 [46]. Viral binding is mediated by TMPRSS2, a human protease, that cleaves S antigen into the S1 subunit, the receptor binding site, and S2, the mediator of viral fusion with host cell membranes [47]. Upon fusion the virus is internalized through the EP pits that join the early and late endosomes, reaching the lysosomes. The later, link the EP to autophagy via autolysosomes (autophagosomes fused with lysosomes) (**Figure 2**).

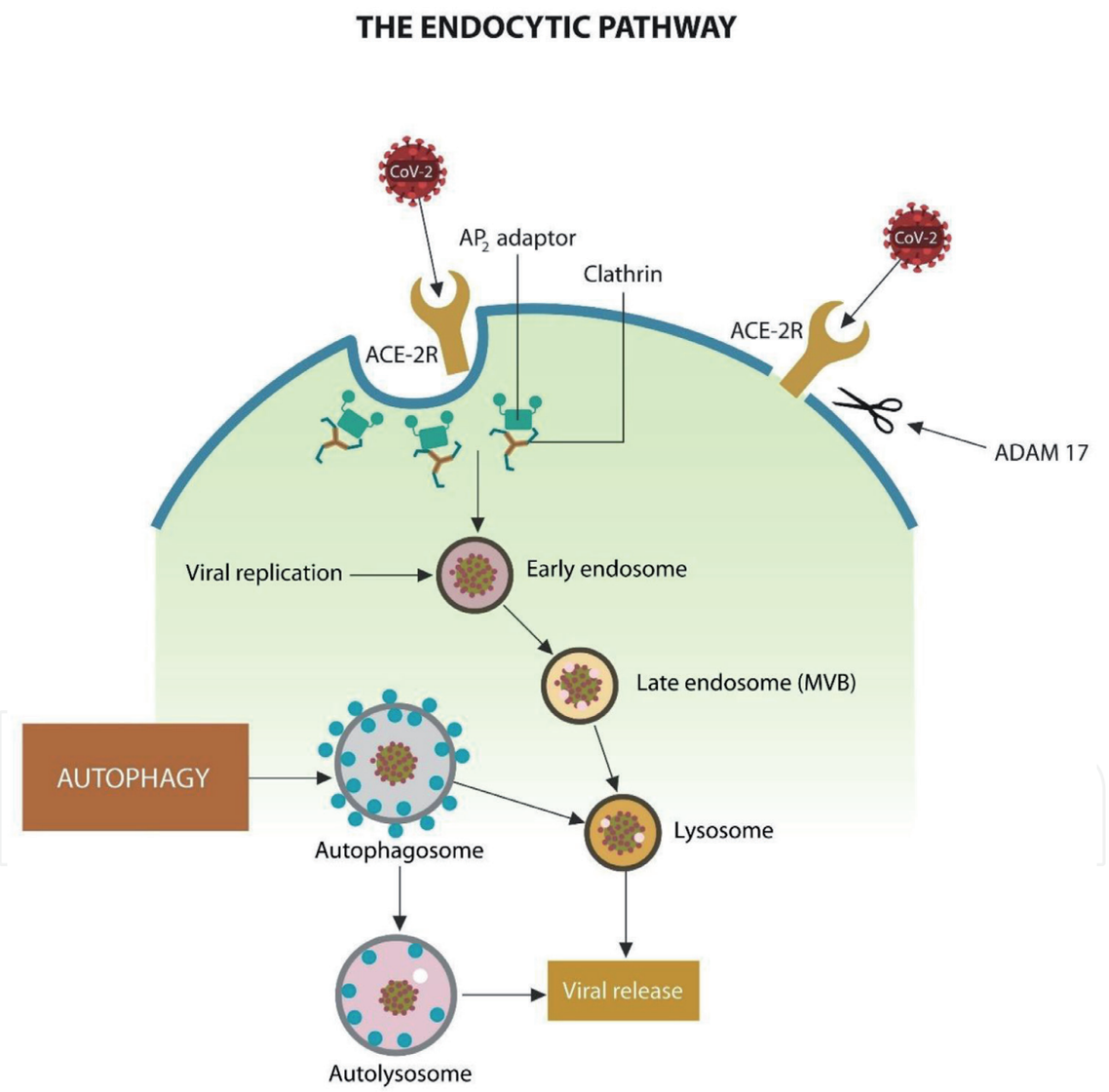

Figure 2.
Upon receptor binding and fusion, SARS-CoV-2/ACE-2 complexes enter human cells through the endocytic pathway (EP) pits early and late endosomes that subsequently join the lysosomes. Lysosomes link the EP to autophagy as authophagosomes (that can also carry the virus) fuse with the lysosomes, engendering the autolysosomes. Viruses are released from the endoplasmic reticulum - Golgi intermediate compartment (ERGIC) (not shown) to the cell surface, either individually or packed in extracellular vesicles (EVs). Viruses connected to ACE-2 receptors that are not endocytosed are shed by ADAM17. Both endocytosis and shedding contribute to ACE-2 downregulation, a marker of COVID-19 critical illness.

The SARS-CoV-2 protein–protein interaction studies have reported that 40% of viral proteins interact with human EP, indicating that vesicular trafficking plays a crucial role in COVID-19 pathogenesis [24]. In addition, several viral proteins usurp mitochondria and autophagy, cellular systems associated with host antiviral defenses [48]. Indeed, the SARS-CoV-2 interactome revealed that the virus hijacks both the mammalian target of rapamycin complex 1 (mTORC1), the master regulator of autophagy, and the E3 ubiquitin ligases in the outer mitochondrial membrane [24].

Upon release from EP into the cytosol, the SARS-CoV-2 virus replicates and assembles in the endoplasmic reticulum - Golgi intermediate compartment (ERGIC) from which the viral progeny is released at the cell surface [49].

4. The SARS-CoV-2/ACE-2 attachment

Novel studies have reported that the S antigen of SARS-CoV-2 virus attaches with high affinity to ACE-2 receptors, promoting oxidative stress by several mechanisms, including ANG 1–7 downregulation, ANG II accumulation and NMDRs or AT-1Rs overstimulation (**Figure 1**) [49–54].

Aside from the S antigen, several other SARS-CoV-2 proteins interact directly with the human molecules, disrupting numerous pathways, including EP, epigenome, mitochondria and autophagy (**Table 2**).

SARS-CoV-2 proteins	Human proteins	References psychiatric pathology
NSP4, NSP8, ORF9C	Mitochondrial dysfunction/oxidative stress	[55]
NSP2, NSP6, NSP7, NSP10, NSP13, NSP15, ORF3A, E, M, ORF8	Endocytic pathway (EP)	[56]
NSP6, ORF9C	Sigma receptors, Autophagy	[57]
NSP5, NSP8, NSP13, E	Epigenome	[58, 59]

Table 2.
The SARS-CoV-2 non-S antigen interactions with human proteins.

Both the S antigen and non-S-induced molecular changes affect molecular pathways previously associated with schizophrenia and autism. For example, excessive NMDAR activation and externalization of phosphatidylserine (PS) on the outer leaflet of plasma membrane was documented in both COVID-19 critical illness and schizophrenia [60]. This is relevant because PS exposure has been linked to dysregulated immunosuppression and the activation of coagulation cascade, changes associated with severe COVID-19 and some psychiatric disorders [61, 62]. With the same token, NMDAR/PS exposure facilitates SARS-CoV-2 endocytosis via the EP [63–65]. Interestingly, PS externalization was associated with schizophrenia as it inhibits monoamine oxidase B (MAO-B), a dopamine (DA) metabolizing enzyme [66]. Loss of MAO-B with subsequent DA upregulation is believed to trigger psychosis, linking PS exposure to severe psychiatric conditions. Furthermore, other studies have associated normal aging with EP upregulation, likely explaining the increased risk of COVID-19 complications in elderly [67].

5. ACE-2 downregulation

The SARS-CoV-2 fusion with host cellular membrane occurs at the level of EP pits, structures comprised of the clathrin heavy chains and adaptor protein 2 (AP2), molecules altered by both schizophrenia and the psychotropic drugs [25, 68–70] (**Figure 2**).

The SARS-CoV-2/ACE-2 complexes that are not endocytosed, are shed by ADAM17, contributing to ACE-2 downregulation and increased COVID-19 severity. The exacerbation of SARS-CoV-2 infection is likely the result of virus/ACE-2 complexes dissemination throughout the body via the circulatory system, increasing infectivity (**Figure 3**) [71].

Novel studies have shown that oxidative stress can directly activate ADAM17, triggering ACE-2 downregulation [72, 73]. This takes place as NMDARs interacts with dopamine 1 receptors (D1Rs) activating ADAM17 to excessively cleave ACE-2 from the cell membranes [74–76]. Moreover, ADAM17 can be activated directly by viral proteins NSP6 and ORF9C interaction with sigma-1 receptors [24, 77] (**Table 2**). Furthermore, PS exposure at the cell surface facilitates ACE-2 downregulation, suggesting that the virus may utilize multiple mechanisms to lower this protein and enable infectivity [78].

Another novel study found that ACE-2 contains a calmodulin-binding site, implicating calcium in ADAM17 activation and COVID-19 critical illness [79, 80].

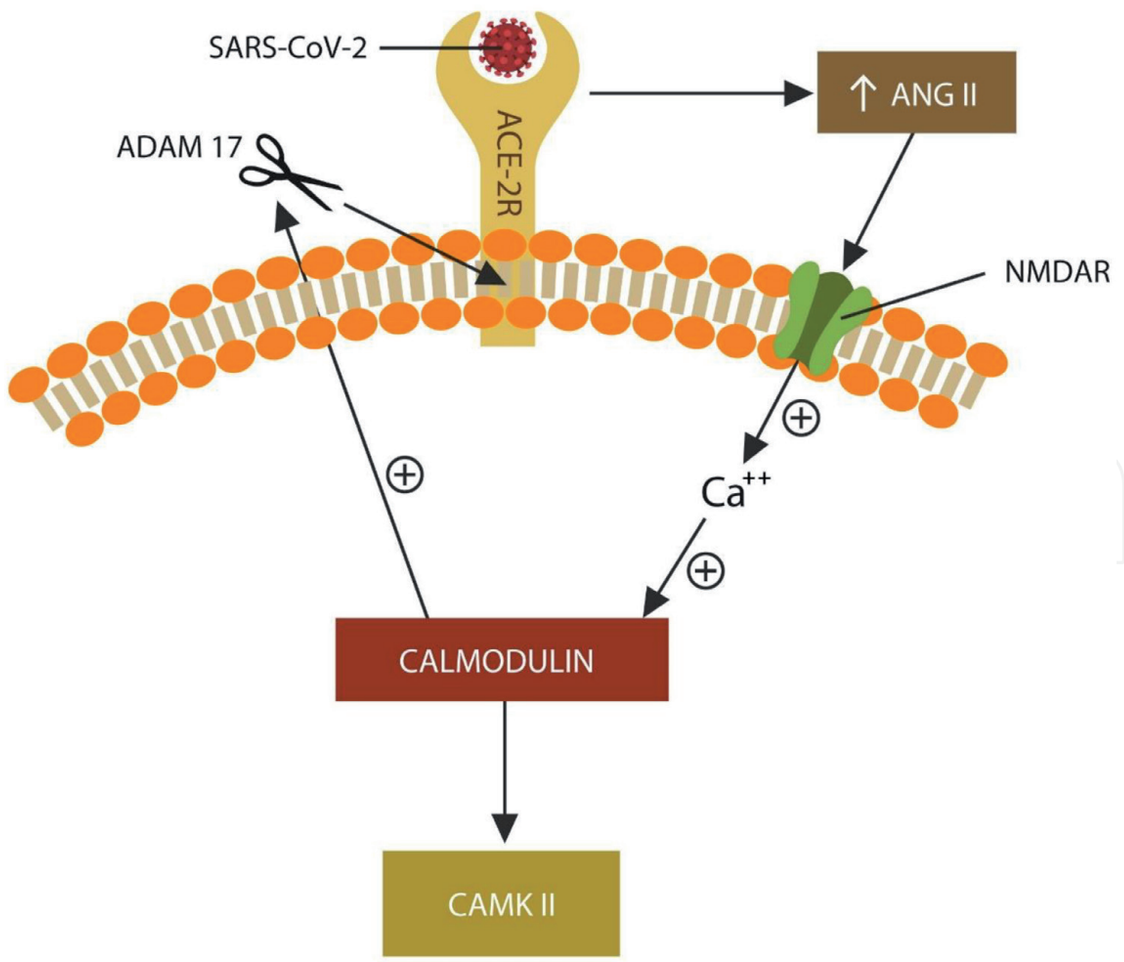

Figure 3.
Activation of ANG II-NMDAR axis results in intracellular calcium influx and calmodulin upregulation. Calmodulin-activated ADAM17 orchestrates the shedding of ACE-2/SARS-CoV-2 complexes, leading to ACE-2 downregulation and high infectivity by ACE-2/SARS-CoV-2 circulatory dissemination.

Indeed, it was established that intracellular calcium influx via NMDARs upregulates calmodulin, activating ADAM17 (**Figure 3**) [81, 82]. On the other hand, calmodulin antagonists, including psychotropic drugs amitriptyline, phenothiazines and melatonin, inhibit ACE-2 downregulation and the odds of COVID-19 complications [83]. In addition, recent studies found that SARS-CoV-2 could activate calcium/calmodulin-dependent protein kinase II (CAMK II), linking the virus further to excitotoxicity (excessive intracellular calcium) [23].

Taken together, ADAM17 promotes ACE-2 downregulation via oxidative stress mediated by NMDARs-upregulated intracellular calcium, mechanisms involved in schizophrenia, drug addictions and COVID-19 critical illness [83–86].

6. COVID-19: a catalyst for novel psychiatric paradigms - part 2

6.1 The virus and madness

The connection between viruses, and psychiatric disorders has been around for many centuries. In the ancient world, Thucydides reported "total and immediate loss of memory" in the survivors of "plague of Athens", a disease suggestive of viral encephalitis [87, 88]. In our time, MRI studies have associated herpes simplex encephalitis, a condition marked by amnesia, with specific neuroimaging markers, linking viruses to cognition [89]. In addition, novel genetic studies have demonstrated that the HK2 retrovirus, frequently detected in the genome of drug addicts, was an ancestral pathogen incorporated into human DNA [90]. Over the past century, numerous studies linked in utero or early postnatal viral infections with the development of schizophrenia and autism later in life [91]. For example, women pregnant during the 1964 rubella epidemic in the United States gave birth to offspring that frequently developed autism or schizophrenia, suggesting that other viruses, probably including COVID-19, may have similar outcomes [92, 93]. In addition, obsessive–compulsive disorder (OCD), schizophrenia, attention deficit hyperactivity disorder (ADHD) and Tourette syndrome were traced to prenatal viral infections [94]. Neurodegenerative disorders, especially Parkinson's disease (PD), were documented to surge after prior pandemics, including the 1918 influenza, suggesting that COVID-19 may promote neurodegeneration [95]. On the positive side, the SARS-CoV-2 virus may prompt the development of novel PD therapies, including angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEi) that have demonstrated efficacy in animal models [96].

Aside from linking prenatal viral exposure to severe psychiatric illness, several new studies reported that dormant CNS viruses could also engender this pathology [97]. For example, a recent report found that compared to controls, patients with schizophrenia demonstrated higher titers of Borna disease virus (BDV) immune complexes [98]. Others have connected influenza A, varicella-zoster, herpes simplex, hepatitis C and human immunodeficiency virus with the development of serious psychiatric disorders [99].

Autoantibodies against NMDARs, demonstrated in some schizophrenia patients, were recently found to be the result of molecular mimicry between the M2 protein of influenza A virus and NMDARs [100, 101]. Indeed, several large epidemiological studies found increased prevalence of autoimmune diseases in patients with schizophrenia, indicating that autoantibodies may be the result of either molecular mimicry or virus-induced modifications in human proteins [102]. For example, the molecular resemblance between an H1N1 influenza antigen and human hypocretin molecule triggers narcolepsy as virus-induced hypocretin modification may elicit autoantibodies [103]. Along these lines, the NMDAR partial

antagonist, memantine, utilized in Alzheimer's disease (AD), was found to possess immunosuppressant properties [39, 103, 104]. Indeed, prior studies have demonstrated memantine efficacy against Trypanosoma cruzi, a disease with established autoimmune pathogenesis [105].

Untreated patients with schizophrenia were reported to be at high risk of COVID-19 complications, probably due to SARS-CoV-2-associated neuroinflammation, an established risk factor of many psychiatric disorders. On the other hand, psychotropic drugs with anti-inflammatory properties may lower the SARS-CoV-2-mediated neuroinflammation, explaining the protective effects of these agents [24, 106].

6.2 COVID-19 and acquired antioxidant defects

According to the two-hit paradigm presented here, the COVID-19 prognosis is likely determined by the status of premorbid redox reserves, especially those comprised of the antioxidant enzymes G6PD and GPX. These proteins maintain homeostasis by neutralizing ANG II-activated NADPH oxidase (NOX) [107]. NOX upregulation was documented in patients with neurodegenerative disorders, schizophrenia, and suicidal behaviors, linking CNS pathology to redox system failure [108–110].

G6PD is a potent antioxidant enzyme that lowers NOX by upregulating the synthesis of NADPH and glutathione (GSH) [111]. Conversely, G6PD deficiency was associated with hemolysis and endothelial dysfunction caused by lower GSH and increased oxidative stress [111].

We surmise that the SARS-CoV-2 virus engenders acquired deficits of G6PD and GPX via ANG II-aldosterone upregulated NOX [112] (**Figure 4**). When COVID-19-induced deficiency of antioxidant enzymes occurs on the background of a hereditary G6PD deficit (observed in some populations with ancestral exposure to malaria), the resultant redox failure trigger COVID-19 critical illness [113] (**Figure 4**).

Several recent studies have supported this model as they established that G6PD deficient individuals, including many African Americans, are more likely to develop COVID-19 critical illness [6, 7, 114–116]. Moreover, G6PD deficiency was associated with cardiovascular disease, hypertension, liver fibrosis and iron dyshomeostasis, indicating the importance of redox balance in this pathology [117–121].

6.2.1 Malaria and COVID-19 prognosis

Malaria is an old enemy of mankind that throughout the past centuries exacted a heavy toll on the population of Africa and the surrounding regions. Residents of these areas have gradually developed phenotypes of plasmodium-resistant erythrocytes, including G6PD deficiency, thalassemia, and hemoglobin C, to protect against malaria [122]. Although these modified red blood cells may block plasmodial ingress, individuals with these changes are more susceptible to hemolysis and iron-mediated oxidative stress that in turn promote infections, hypertension, cancer and neuropsychiatric disorders [123–126]. Indeed, both *Plasmodium falciparum* and the SARS-CoV-2 virus induce redox dysfunctions conducive to these pathologies.

Neuropsychiatric manifestations of malaria have been known since the ancient era however, they were more thoroughly studied only in World War I when French Army physicians encountered malaria during the campaign in Northern Greece [127–129]. More recent studies demonstrated that ROS play a major role in the pathogenesis of malaria and the CNS manifestations of this infection. For example, excessive ROS were shown to directly activate nucleotide-binding oligomerization domain-like receptor family, pyrin domain-containing-3 (NLRP3) inflammasomes, molecular

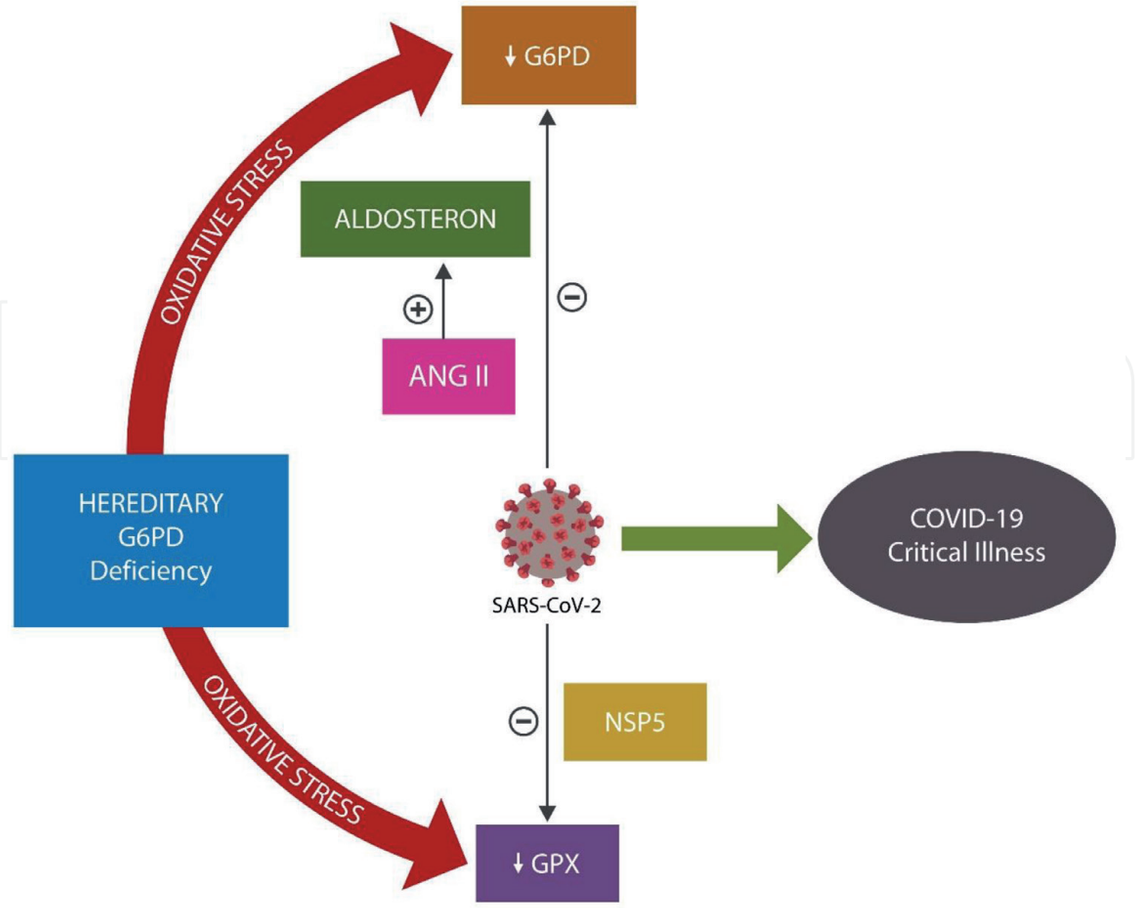

Figure 4.
The SARS-CoV-2 virus causes oxidative stress by inhibiting both GPX (directly) and G6PD (indirectly via ANG II and aldosterone-upregulated NOX). Individuals with hereditary G6PD deficiency are at higher risk for developing COVID-19 critical illness as the loss of antioxidant enzymes is more profound and oxidative stress higher.

structures involved in numerous pathological processes, including t psychiatric disorders [130, 131]. Interestingly, some antipsychotic drugs, including clozapine, function as NLRP3 inhibitors, indicating anti-neuroinflammatory properties [132]. The SARS-CoV-2 interactome established that viral protein OPR3a can activate NLRP3 directly, suggesting a pathway for virus-induced neuroinflammation [133, 134].

Several studies reported that *Plasmodium falciparum*-infected red blood cells externalize PS, a phenomenon observed in severe COVID-19 illness [135]. On the other hand, CPZ was demonstrated to bind PS, promoting eryptosis (elimination of infected red blood cells) with improvement of malaria symptoms [136, 137]. Interestingly antimalarial drugs, chloroquine and hydroxychloroquine operate by inhibiting the EP, a common mechanism of action with some antipsychotic drugs, including CPZ [138]. Since erythrocytes with externalized PS were also documented hypertension, further studies are needed to clarify the role of PS in illness and eryptosis as a possible therapeutic intervention [138, 139]. Indeed, CPZ has been utilized routinely in the emergency treatment of uncontrolled hypertension, indicating a possible role of eryptosis in addition to the well-established CPZ effects on alpha-adrenergic receptors [140].

6.2.2 Malaria exposure and the risk of COVID-19

Population groups throughout the world with exposure to malaria during the previous centuries were found to be at higher risk of hereditary G6PD deficiency

and antioxidant failure. This background increases the odds not only of viral infections but also of other redox disorders, including hypertension, cancer and cardiac disease. For example, 12.2% of African American males and 4.1% of females are G6PD deficient, indicating a potentially higher risk of COVID-19 complications [141]. Indeed, novel studies found a 2.4 percent higher COVID-19 mortality in African Americans compared to Whites, Asians or Latinos [142].

Moreover, the lower GSH and nitric oxide (NO) levels in African Americans compared to other groups, places this population at higher risk of both hypertension and prostate cancer, suggesting that the SARS-CoV-2 infection may precipitate these complications [143–149]. In this regard, African Americans with COVID-19 should be routinely assessed for G6PD deficiency and supplemented with the widely available antioxidant, N-acetylcysteine [150].

Oxidative stress was demonstrated to directly trigger hypertension by resetting the CNS baroreflex, therefore the G6PD-deficient individuals could be more prone to COVID-19-related cardiovascular complications [151]. On the other hand, ARBs and ACEi lower ANG II-mediated ROS, likely averting these complications [152–157]. Indeed, the lower utilization of ARBs and ACEi in the treatment of hypertensive African Americans may place this population at higher risk of COVID-19 critical illness [158]. Although numerous clinical trials supported the efficacy of ARBs and ACEi in African Americans, these drugs are rarely utilized in this population as an initial therapeutic options [158, 159]. This is significant as both ARBs and ACEi appear to lower COVID-19 mortality rate, probably by dampening oxidative stress-ACE-2 downregulation. For example, a novel study found that COVID-19 patients treated with ACEi or ARBs at the time of initial infection had fewer unfavorable outcomes and lower mortality rate compared to individuals unexposed to these drugs [160].

Taken together, the SARS-CoV-2-upregulated ANG II, triggers hypertension and cardiovascular disease by augmenting oxidative stress and altering the baroreceptor setting. Individuals with G6PD deficiency are at increased risk of both hypertension and COVID-19 critical illness, indicating alignment with the two-hit paradigm presented here.

7. Conclusion

The COVID-19 pandemic has exacerbated the disease course in many psychiatric patients as mandatory social isolation and decreased frequency of therapeutic meetings promoted fear and uncertainty in this fragile population. The restrictive measures associated with the pandemic have often led to decreased medication adherence, increased depression, anxiety and substance use disorders, often contributing to unfavorable outcomes.

On a positive note, the SARS-CoV-2 virus may be a catalyst for a better understanding of the role of viruses in the pathogenesis of psychiatric illness. As SARS-CoV-2 (and probably other viruses) utilize the molecular machinery involved in severe psychiatric disorders, the clarification of these mechanisms may help with the development of better therapies. Indeed, the EP and antioxidant enzymes may become the new psychiatric paradigms, expanding the current dopamine and serotonin models to include viruses and microbes in psychopathology.

DOI: http://dx.doi.org/10.5772/intechopen.96940

Author details

Adonis Sfera[1*], Carolina Osorio[2], Jose E. Campo Maldonado[3], Afzaal Jafri[1], Aaron D. Chokka[1], Carlos Manuel Zapata Martín del Campo[5] and Zisis Kozlakidis[4†]

1 Patton State Hospital, San Bernardino, CA, United States

2 Department of Psychiatry, Loma Linda University, Loma Linda, CA, United States

3 Department of Medicine, The University of Texas Rio Grande Valley, Edinburg, TX, United States

4 International Agency for Research on Cancer, World Health Organization, Lyon, France

5 National Institute of Cardiology "Ignacio Chávez", Mexico City, Mexico

*Address all correspondence to: dr.sfera@gmail.com

† Where authors are identified as personnel of the International Agency for Research on Cancer/WHO, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/WHO.

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