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COVID-19: Oxidative Preconditioning as a Potential Therapeutic Approach

Rachid Akki,* Nada Fath, and Hicham Mohti

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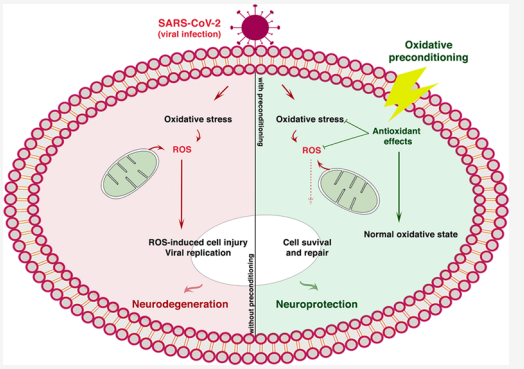
ABSTRACT: This Article summarizes the likely benefits of central nervous system oxidative preconditioning in the reduction of COVID-19 based on its putative pathogenesis. The current COVID-19 outbreak caused a pandemic with millions of infected patients and death cases worldwide. The clinical features of severe acute respiratory syndrome coronavirus (SARS-CoV) was initially linked with respiratory disorders, but recent studies have reported alterations of neurological and cerebrovascular functions in COVID-19 patients. The main viral infection features are related to cell death, inflammation, and cytokine generation, which can be associated with the dysregulation of redox systems or oxidative stress. However, until now, there is no available and effective therapeutic approach. Thus, it is necessary to search for care and adequate protection against the disease, especially for susceptible and vulnerable groups. Preconditioning, a well-known antioxidative stress and anti-inflammatory approach, is protective against many neurological age-related disorders. COVID-19 severity and morbidity have been observed in elderly patients. The aim of the present study is to elucidate the possible protective role of oxidative preconditioning in aged patients at high risk of developing severe COVID-19 complications.



KEYWORDS: *Preconditioning, SARS-CoV-2, COVID-19, antiviral, oxidative stress, CNS*

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1. INTRODUCTION

COVID-19 has been described for the first time as a pneumonia of unknown cause by Zhu et al.[1] who reported the results of a study of three cases who were admitted to the hospital in Wuhan and diagnosed with severe pneumonia at an early stage of the outbreak. Patient clusters were diagnosed with acute respiratory syndrome.[2] Typical clinical symptoms at onset of illness are fever, dry cough, breathing difficulties (dyspnoea), and pneumonia; fewer common symptoms were sputum production, headache, hemoptysis, myalgia or fatigue, and diarrhea,[1−3] but respiratory distress worsened a few days later and required mechanical ventilation. This respiratory failure has been linked to alveolar damage,[2] and the novel coronavirus, named 2019-nCoV, was reported as the likely etiological agent of the viral pneumonia[1] and may result in death.[3]

However, epidemiological studies confirmed that the disease can be transmitted by human-to-human contact[4] and reported the potential of global spread.[5,6] By October 13, 2020, SARS-CoV-2 had infected more than 38 028 000 people around the world and killed more than 1 085 000.

The complete genome sequences obtained at an early stage of the outbreak are similar to those of SARS-CoV, the virus that caused the SARS epidemic in 2003, and use the same receptors, angiotensin converting enzyme II (ACE2), to enter into the human cell.[2] In addition to the airway epithelia, ACE2 is widely expressed throughout the human body in the kidneys, intestine, lungs, vascular endothelia, and central nervous system (CNS).[7] This widespread expression and distribution of ACE2 receptors in the human brain, on the surface membrane and in the cytoplasm of neurons, but also in glial cells determines the neurotropism of SARS-CoV-2[7] and indicates that this virus may cause some neurologic manifestations through direct or indirect mechanisms.

In the CNS, SARS-CoV-2 triggers neuroinflammatory events, which may be a potential cause of the nervous system abnormalities observed in COVID-19 patients. Published data attributes those events initiated by viral infections mainly to ROS production and oxidative stress.[8−11] Herein, we provide evidence indicating that oxidative preconditioning will have supportive utility in alleviating the impact of COVID-19 induced alteration of tissue homeostasis and integrity that

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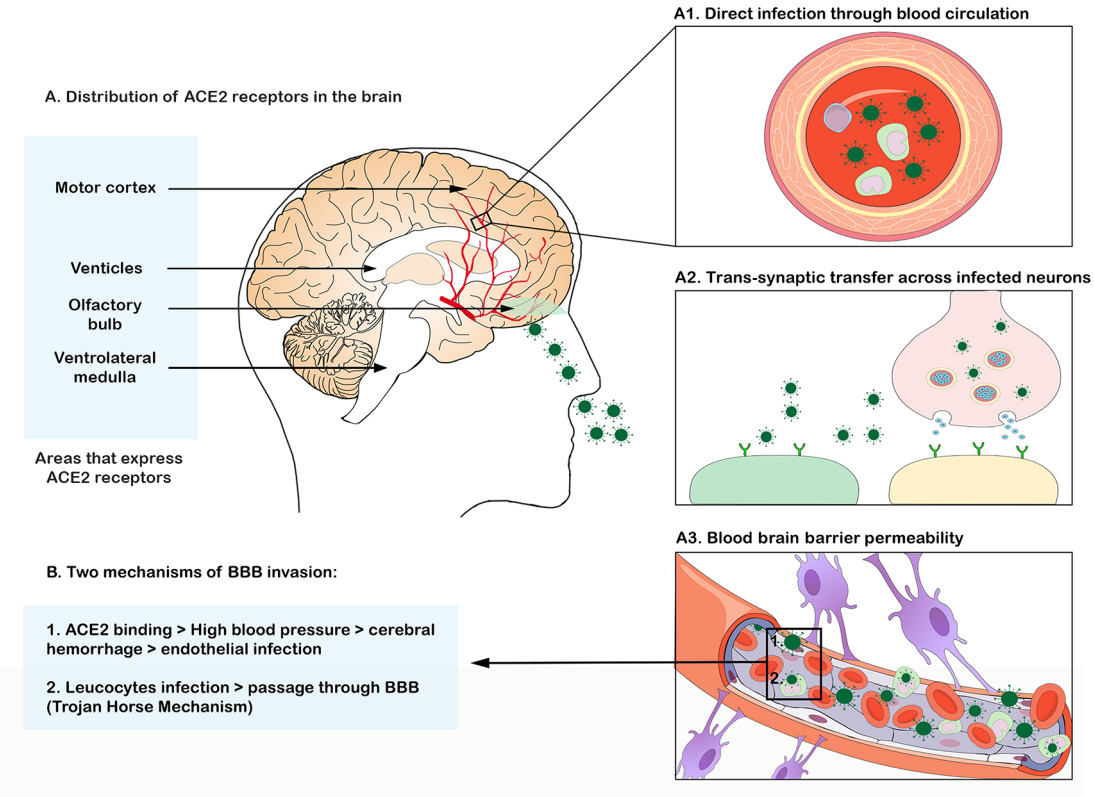

Figure 1. Distribution and expression of ACE2 in the brain and the possible pathways of SARS-CoV-2 neuroinvasion (A). The virus may enter into the brain through the blood circulation (A1), neuronal pathway (A2), olfactory bulb or via the permeable BBB (A3). It may bypass the BBB either via endothelial infection or leukocyte infection (B). Created by author N. Fath.

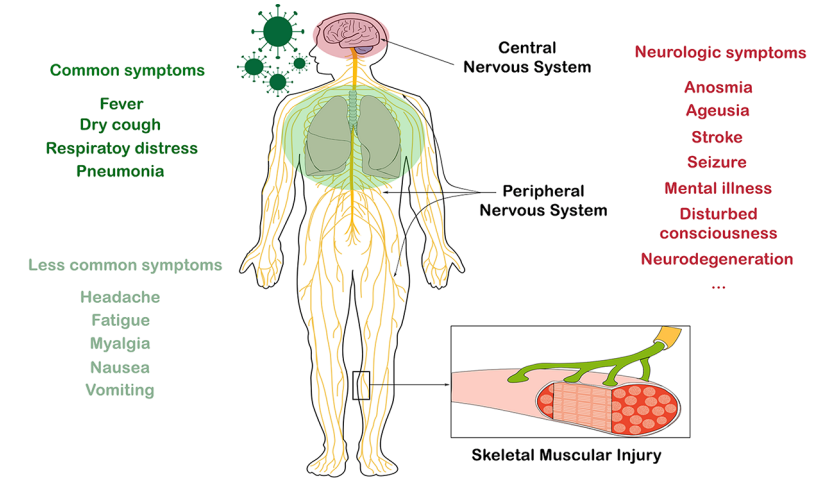

Figure 2. COVID-19 common symptoms and neurologic manifestations. SARS-CoV-2 causes three types of neurologic symptoms depending on its location in the nervous system: CNS injury, PNS injury, and skeletal muscular injury. In addition to its common symptoms, the virus induces multiple neurologic manifestations in the early stage of the disease. Created by author N. Fath.

provokes organ failure (i.e., lung, heart, especially brain). Here, we focus on brain.

2. PATHOGENESIS OF COVID-19 AND CNS ALTERATIONS

2.1. Neuroinvasive Potential of SARS-CoV-2. As with the severe acute respiratory syndrome coronavirus (SARS-CoV)[12,13] and Middle-East respiratory syndrome coronavirus (MERS-CoV),[14] SARS-CoV-2 may invade the CNS through the hematogenous or retrograde neuronal route. There is growing evidence of neurological complications and disease in patients with COVID-19. The virus may reach and affect the CNS through several possible pathways (Figure 1a): Direct infection injury through the blood circulation, where the vascular endothelium in the cerebral circulation express ACE2 receptors, by the neuronal pathway,[7,15] by trans-synaptic transfer across infected neurons,[15] or by an additional pathway near the olfactory bulb, through the cribriform plate.[16]

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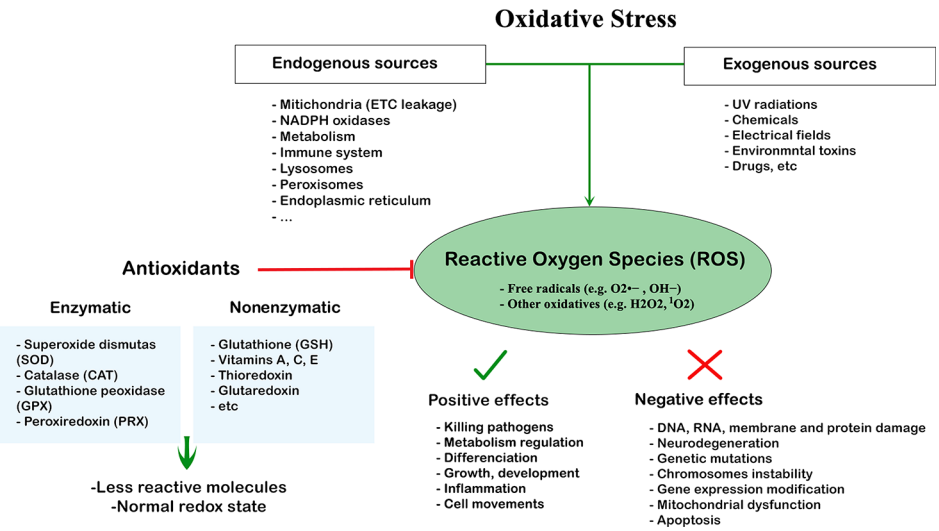

Figure 3. Schematic presentation of the endogenous and exogenous sources of ROS, their effects on the organism, and the action of antioxidant defense mechanisms. Created by author N. Fath.

Furthermore, there are two possible mechanisms for SARS-CoV-2 spread across the blood−brain barrier (BBB) (Figure 1b); the binding to ACE2 receptors may cause abnormally elevated blood pressure and increase the risk of cerebral hemorrhage and may also affect the BBB integrity and enter the CNS by attacking the vascular endothelial cells.[16] The second mechanism is through the Trojan horse mechanism, which is the infection of leukocytes that pass through the BBB.[15] The systemic inflammation that characterizes COVID-19 likely increases the permeability of the BBB, thereby allowing infected immune cells, cytokines, and possibly virus to pass into the CNS as previously described for the SAS-CoV virus.[17−19]

2.2. Neurologic Symptoms in COVID-19 Patients. Some COVID-19 patients reported neurologic symptoms, mainly headache, loss of sense of smell (anosmia), and loss of sense of taste (ageusia),[20,21] nausea, and vomiting, which may be a sign of a the likely neuroinvasive potential of the virus.[22] The first reported case of meningitis/encephalitis associated with SARS-CoV-2 was a 24-year-old patient diagnosed with viral pneumonia and aseptic encephalitis.[23] The particularity with this case is that SARS-CoV-2 RNA was not detected in the nasopharyngeal swab, but the RT-PCR test for SARS-CoV-2 using the patient's cerebrospinal fluid (CSF) specimen was positive, which illustrates its potential to cause CNS damage.[24] A handful of case reports have described neurological complications in patients with COVID-19,[25−28] but the extent of the viral infection in the CNS is yet to be understood.

The first study that investigated the neurotropic effect of SARS-CoV-2 infection reported that patients with COVID-19 commonly have neurologic manifestations, that were more common in severe infections, with an early onset of 1−2 days after infection.[25] Some patients even develop COVID-19-related symptoms only after showing neurologic symptoms. The study involved 214 patients of which 36.4% reported neurologic symptoms including headache, disturbed consciousness, and paresthesia.[25] Abnormalities were detected in three different locations (Figure 2). The CNS, manifested by headache, impaired consciousness, acute cerebrovascular disease, and seizure; the peripheral nervous system (PNS), manifested by impaired taste, smell, vision, and nerve pain; and finally skeletal muscular injury manifestations, which may be caused by the significantly elevated proinflammatory cytokines in serum.[25] CNS manifestations were the main form of neurologic injury symptoms in severely affected patients.

Moreover, in addition to this study conducted in Wuhan, China, systemic studies in France,[27] Germany,[20] and India[29] also reported the previously described neurologic manifestations in COVID-19 patients admitted to the intensive care unit (ICU)[21,25] in addition to coma, seizure, and encephalopathy.[23,26]

In another study of the ICUs from multiple institutions in Italy, COVID-19 patients showed acute neurological symptoms, dominated by acute ischemic infarcts and intracranial hemorrhage.[28] The most common neurological symptoms were altered mental status in 59% of patients and ischemic stroke in 31% of patients. Additionally, postmortem examination of brain tissue at autopsy revealed the presence of edema and partial neuronal degeneration,[4] neuronal necrosis, and glial cell hyperplasia,[15] confirming the effect of the SARS-CoV-2 on the brain.

Taken together, this data suggest that the neurological symptoms may be the first indication to find the hidden SARS-CoV-2. Most neurologic manifestations occurred early in the illness (the median time to hospital admission was 1−2 days); thus, clinicians should suspect COVID-19 as a differential diagnosis to avoid delayed diagnosis that may aggravate the actions of the virus.

3. OXIDATIVE STRESS AND VIRAL INFECTION

3.1. Oxidative Stress. Oxidative stress occurs as a consequence of life in an oxygen-rich environment, where oxygen radicals and other activated oxygen species (ROS) are produced as byproducts of aerobic metabolism (Figure 3). There are four major enzyme systems that produce ROS in mammalian cells: NADPH oxidases, xanthine oxidase, uncoupled NO synthase, and the mitochondrial electron transport chain (ETC). The predominant intracellular sources are ETC and NADPH oxidases.[30] NADPH oxidases catalyze the transfer of electrons from NADPH to molecular oxygen via catalytic subunits, the nicotinamide adenine dinucleotide phosphate oxidase (NOX) protein family, producing $O2^{\bullet-}$

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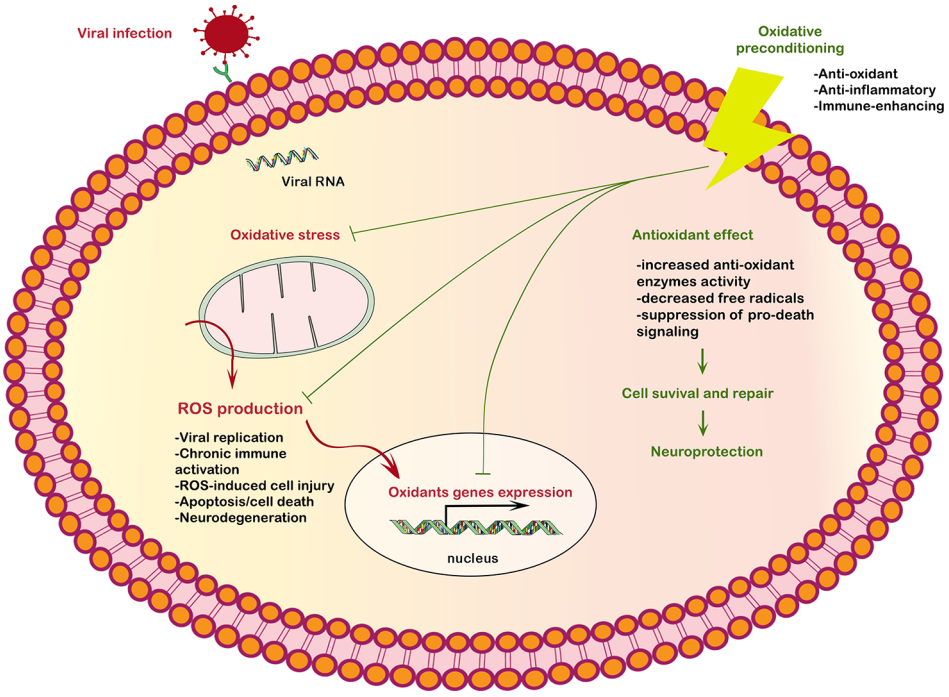

Figure 4. SARS-CoV-2 viral infection triggers ROS production and oxidative stress in the cell. This viral stress can be attenuated by oxidative preconditioning that induces metabolic changes favoring cell adaptation, repair, and survival. Created by author N. Fath.

and H_2O_2.[30,31] The NOX family consists of seven members (NOX1−5 and DUOX1−2), and isoforms have different regulation and specific subcellular localizations. They exist in the plasma membrane as well as in intracellular membranes of the nucleus, mitochondria, and endoplasmic reticulum and generate distinct ROS.[31]

To neutralize excess ROS and minimize the adverse effects caused by stress and damage caused by oxygen, cells, tissues, organs, and organisms use various antioxidant defense systems (Figure 3) for adaptation, modulation, damage removal, replacement, and repair to maintain the redox system homeostasis.[32] They are divided into enzymatic antioxidants, which include superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), thioredoxin reductase,[32] and nonenzymatic antioxidants vitamins C, A, and E, glutathione, and thioredoxin.[30] Antioxidant isoforms have been recognized in the cytosol, mitochondria, endoplasmic reticulum, peroxisomes, and extracellular space.

3.2. Viral Infection. It is known that respiratory viral infections are associated with many pathophysiological processes such as inflammation, cytokine production, and cell death, which can be attributed to a redox imbalance, ROS overproduction, or oxidative stress (OS).[33]

In a study of cases with confirmed SARS-CoV-2 infections, all patients had pneumonia and some of them developed lymphopenia after viral infection. Critically ill patients admitted in ICUs showed higher plasma levels of IL2, IL7, IL10, and TNFα. This higher concentrations of proinflammatory cytokines in plasma suggests an association between cytokine storm and disease severity.[3] Furthermore, it has been reported in the severe subgroup that patients with neurologic manifestations had lower lymphocyte and platelet levels with higher nitrogen levels in urea compared with patients without CNS damage.[16,25] Those abnormalities suggest the immunosuppression phenomenon in COVID-19 patients with CNS manifestations, especially in the severe subgroup.

In the other hand, ROS producing and scavenging machineries have been hypothesized to be crucial for viral replication, virion release, and onset of related diseases.[33] In addition to coronaviruses, other respiratory viruses display specific clinical syndromes such as bronchiolitis and pneumonia, but also common clinical manifestations. These infections are usually accompanied by exacerbated inflammation, triggered in general by the induction of ROS-generating enzymes, ROS production, and changes in redox homeostasis in the infected cells.[8,10,33] The link between inflammation and OS is well established. Moreover, the accumulation of ROS and alteration of scavenging systems leads to the development of OS and chronic activation of immune responses and inflammation, which may cause endothelial dysfunction and tissue injury.[34]

ROS are highly reactive molecules that are produced as a result of the molecular oxygen reduction of species such as superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH^-).[30,35] In addition to their significant cell-signaling ability to regulate the phenotype and function of immune cells, ROS production has a crucial role in the fight against invading microorganisms. Intracellular ROS induce stress and contribute to innate immune activation[35] but also have a critical role in chronic inflammation in the respiratory tract.[36]

It is known that oxidative stress can initiate immune response. It promotes the passage of inflammatory cells through the endothelial barrier because it opens the inter-endothelial junctions. But these inflammatory cells summoned to help in the clearance of pathogens also cause tissue injury. Pronounced immune activity causes a cytokine storm and may lead to tissue damage. Moreover, chronic or prolonged ROS production is considered central to the genesis and progression of inflammatory disease.[37] However, the mechanism under-

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lying oxidative stress following viral infection is yet to be understood.

Many studies reported by Khomich and colleagues have reported signs of enhanced production of ROS in all respiratory viral infections.[33] Marked increases in DNA, lipid, and protein oxidation products in blood plasma and urine were reported in patients infected with influenza A (H1N1),[38−40] in addition to increased levels of ROS in lung tissues of deceased patients.[41] In addition to influenza, Khomich et al. have reported increased ROS production in other respiratory viruses such as human respiratory syncytial (HRSV), human rhino (HRV) and coronaviruses.

Furthermore, investigations of the possible implication of oxidative stress in the progression of SARS-CoV disease and its severity in patients with the viral infection showed that the pathogenesis can favor an increase in oxidative stress that exacerbates neuroinflammation.[42] Although ROS are known to help in the clearance of some respiratory infections through the induction of innate immune responses, higher concentrations are injurious and the viral infection may disrupt the antioxidant defense pathways against ROS and lead to unbalanced oxidative-antioxidant status.[43] Thus, antioxidant therapies could be a good way to improve subsequent oxidative cell damage and disease consequences. Furthermore, oxidative and/or nutritional preconditioning and antioxidant supplementation may have a positive effect in alleviating the consequences of the viral infection.

4. RATIONAL USE OF OXIDATIVE STRESS PRECONDITIONING

Oxidative preconditioning has indirect antiviral action but is not viricidal, due to its antioxidative stress, anti-inflammatory, and immune enhancing properties (Figure 4). Recent reports[44,45] support a rationale for nutritional preconditioning use in viral disease. In addition, preconditioning properties as such antioxidant, anti-inflammatory, and immune enhancing effects support its potential implication in attenuating COVID-19 infection.[46−48] Furthermore, preconditioning induces protective effects through activation of a panoply of genes and pathways involved in cell survival and repair, suppressing pro-death signaling, and can stimulate metabolic changes congruent with survival.[49−52]

The antioxidative stress actions of preconditioning cooperate with its anti-inflammatory effects by activation of Akt and ERK1/2 as well as downregulation of NF-kB signaling.[53] In addition, preconditioning increases the activity of antioxidant enzymes that function as scavengers such as catalase and decreases generation of free radicals by pro-oxidant enzymes such as nitric oxide synthase.[54−56] ROS are generated constantly by viral infections and their replication.[57] In addition, central mediators implicated in preconditioning have been observed in cellular adaptation to both viral stress and hypoxia. These cellular adaptations leading to neuroprotection in the CNS has been triggered by viral infection and hypoxia.[49]

Preconditioning with the small molecule tilorone induced a significant reduction of 80% in infarct size in rat models following spinal cord injury induced by ischemia.[58] Tilorone has been developed for the first time as antiviral immunomodulator, which provide evidence of possible link between antiviral defense and hypoxic preconditioning signaling.[49] In addition, interferon type I activation has been involved not only in preconditioning, but also in tumor survival and antiviral defense.[59] Preconditioning induced activation of interferon signaling occurs through the TLR3-independent pathway which depends on interferon-α and MDAV5.[60]

The innate immune system is equipped with viral infection sensors and provides protective responses.[61] The toll-like receptors (TLRs) and the RIG-I-like receptors (RLRs) play a dominant role in the initiation of subsequent adaptive and appropriate immunity such as T cell and B cell response.[61−63] Thus, targeting endogenous antiviral defense via the use of TLRs for their ability to recognize RNA viruses such as SARS-CoV-2 appears to be a suitable therapeutic approach against viral infection.[64,65]

RNA recognition by the innate immune system in response to viral infection is a key point for the initiation of immunity.[66] Hotz and colleagues showed that in vitro and in vivo preconditioning with a synthetic viral RNA (dsRNA), polyinosinic-polycytidylic acid [poly(I:C)], induced inhibition of RLRs and increased sensitivity of endosomal TLRs, in vitro via increased IFN-β and IL-12 signaling and in vivo through augmenting the activity of MAPK and NF-kB signaling pathways. These changes in pattern-recognition receptor sensitivity elicited by poly(I:C) were also observed in cells exposed to Sendai virus. Thus, preconditioning with dsRNA induced a dynamic adaptation of antiviral innate receptors in response to infection through integration of different antiviral receptors into programmed immune responses and may also serve to reduce the severity of pathological inflammation.[67]

5. AGE-RELATED RISK FACTOR AND COVID-19 INFECTION

The severity and gravity of SARS-CoV-2 infection have been linked with age.[68,69] Recent published research suggests that the mortality rate could be extremely higher in elderly patients compared with young groups.[68] The fatality rate in elderly COVID-19 patients was associated with comorbidities such as hypertension, obesity, cardiovascular disease, and diabetes that exacerbate symptoms and the development of severe neurological disorders.[42,69,70] Furthermore, in elderly patient groups with these comorbidities, the susceptibility to death increased five times compared with younger patients.[71]

In the aging brain, the critical common factor among age-related neurodegenerative diseases is the progressive decline in the physiological function accompanied by increased oxidative stress.[72,73] Also, it has been suggested that accumulated oxidative damage and a weakened antioxidant defense system associated with aging disrupt the redox balance, resulting in augmented ROS production.[74] Literature reports suggested that aging acceleration and the onset of various biological abnormalities were associated with oxidative stress,[75,76] which causes progressive damage over time and subsequently results in aging and death. In addition, age has a powerful effect on susceptibility of cell and tissue to the deleterious impact of oxidative damage and development of various stress age-dependent diseases (i.e., diabetes, stroke, Alzheimer's disease, hypertension, and immune-senescence).[77−80] In a study by Li et al.,[81] patients who developed cerebrovascular disease were significantly older and had more cardiovascular risk factors. They were more likely to have severe COVID-19 disease manifestations.

It is well established that patients with cerebrovascular disease and ischemic stroke present a high risk group for their higher expression for COVID-19 receptor ACE2.[2,70] It has been observed in a rat model undergoing middle cerebral

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artery occlusion (MCAO) that ACE2 expression was upregulated. Moreover, The same result was found in cultures of primary human brain microvascular endothelial cells with type I and II diabetes.[70] In a rabbit model undergoing coronary artery occlusion, preconditioning reduced heart infarction through modulation of angiotensin type 1 receptors.[82] Moreover, in a mouse model infected with measles virus (MV), stress preconditioning promotes brain viral clearance and enhances immune response efficiency.[83] Therefore, as reviewed previously, the susceptibility to viral infection in elderly patients including SARS-CoV-2 not only is associated with the reduction in antioxidant defense, proinflammatory status, and alteration of innate immune system efficiency, but also is due to systemic oxidative stress.[73,80,84]

6. PRECONDITIONING AND SAFETY

One must consider the safety of the use of preconditioning to prevent the exacerbation of COVID-19 symptoms and the high mortality rate in patients with risk factors. As reviewed previously, the susceptibility to viral infection in elderly patients including SARS-CoV-2 is associated with not only the reduction in antioxidant defense and alteration of the innate immune system efficiency but also the systemic oxidative stress.[73,80,84]

In randomized controlled trials, in patients undergoing surgical brain tumors, remote ischemic preconditioning enhanced cerebral perfusion and improved the surgery outcome by reducing the incidence of postoperative brain ischemia in these patients.[85−87] Despite the very high safety profile of preconditioning (i.e., patients with severe carotid artery stenosis),[88] it should be carefully monitored when applied to COVID-19 patients.

7. CONCLUSION

Stress preconditioning exerts regulatory actions on multiple protective pathways including the immune system, inflammatory pathway, cell death regulation, and regulation of oxidative stress. It is important to note that stress preconditioning does not alter or reduce infection incidence, but rather enhances the body adaptive response to various insults including stroke, brain disorders, and viral infection. Moreover, the selection of an adequate preconditioning stimulus that triggers the best outcome in response to a special threat should be taken in consideration. Also there is an urgent need to pay close attention to neurological manifestations and SARS-CoV-2 actions in the brain, as this will offer important insights into treatment and management of the disease.

AUTHOR INFORMATION

Corresponding Author

Rachid Akki − *Department of Plant Protection, National School of Agriculture-Meknes/ENA, Meknès 50001, Morocco;* orcid.org/0000-0001-7653-5480; Email: akki.rachid2011@gmail.com

Authors

Nada Fath − *Compared Anatomy Unit, School of Veterinary Medicine, Hassan II Institute of Agronomy and Veterinary Medicine, Rabat 10000, Morocco; Physiology and Pathophysiology Laboratory, Department of Biology, Faculty of Sciences, Mohamed V University, Rabat BP 8007.NU, Morocco*

Hicham Mohti − *Management and Valorization of Natural Resources, Faculty of Sciences, Moulay Ismail University of Meknes, Meknes BP 11201, Morocco*

Complete contact information is available at: https://pubs.acs.org/10.1021/acschemneuro.0c00453

Author Contributions

R.A. conceived the idea, analyzed and interpreted the data, and drafted the manuscript. N.F. designed the illustrations, analyzed and interpreted the data, and drafted the manuscript. H.M. contributed to the revision and approved the last version.

Notes

The authors declare no competing financial interest.

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