

Putative mechanism of neurological damage in COVID-19 infection

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The recent pandemic of the coronavirus infectious disease 2019 (COVID-19) has affected around 192 countries, and projections have shown that around 40% to 70% of world population could be infected in the next months. COVID-19 is caused by the virus SARS-CoV-2, it enters the cells through the ACE2 receptor (angiotensin converting enzyme 2). It is well known that SARS-CoV-2 could develop mild, moderate, and severe respiratory symptoms that could lead to death. The virus receptor is expressed in different organs such as the lungs, kidney, intestine, and brain, among others. In the lung could cause pneumonia and severe acute respiratory syndrome (SARS). The brain can be directly affected by cellular damage due to viral invasion, which can lead to an inflammatory response, by the decrease in the enzymatic activity of ACE2 that regulates neuroprotective, neuro-immunomodulatory and neutralizing functions of oxidative stress. Another severe damage is hypoxemia in patients that do not receive adequate respiratory support. The neurological symptoms that the patient presents, will depend on factors that condition the expression of ACE2 in the brain such as age and sex, as well as the mechanism of neuronal invasion, the immune response and the general state of the patient. Clinical and histopathological studies have described neurological alterations in human patients with COVID-19. These conditions could have a possible contribution to the morbidity and mortality caused by this disease and may even represent the onset of neurodegenerative activity in recovered patients.

Key words: SARS-CoV-2, COVID-19, ACE2 activity, brain, neurological damage

INTRODUCTION

The appearance of the novel coronavirus (SARS-CoV-2) in late 2019, took the whole world by surprise. It was first observed in Wuhan, Hubei Province, China, but quickly spread across the globe reaching the classification of pandemic by the World Health Organization (WHO). The location of the SARS-CoV-2 outbreak could have been at the Huanan seafood market because the origin of the initial cases showed a history of direct or indirect contact there. The virus was first isolated from a patient on January 7, 2020 (Jiang et al., 2020).

To date it is unknown whether this novel coronavirus originated from wild animals, however, a common ancestor with that of severe acute respiratory syndrome (SARS) was found for the bat coronavirus HKU9-1 (Xu et al., 2020). Both shared the same receptor, therefore the virus was called SARS-CoV-2 and recently WHO named it coronavirus disease 2019 (COVID-19). The high nucleotide identity of the COVID-19 protein S, when compared to other types of SARS-like coronaviruses in the bat (bat-SL-CoVZXC45, bat-SL-CoVZXD21, bat-SL-CoVZXC45) demonstrated high homology (Yuan et al., 2020). There are other animals that could be potential hosts of the virus, such as the

pangolin and snakes (Rothan et al., 2020; Liu et al., 2020). However, the original host of the virus has not been fully clarified. Zoonosis was the initial phase of the epidemic and due to high rates of mutation and recombination by the virus, its rate of transmission from person to person has increased. Also, it has been shown that transmission can occur during the incubation period (Yuan et al., 2020; The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020). Moreover, patients who were discharged and retested by RT-PCR showed to be carriers of the virus (Lan et al., 2020).

However, it should be assessed whether these patients are infectious or not or if they require isolation and if they require treatment. Person-to-person transmission occurs through droplets from coughing or sneezing, close contact, or probable aerosols. The WHO estimated that the R_0 (reproduction number) is 1.4 to 2.5, which means that each infected person can infect between 1.4 to 2.5 individuals (World Health Organization, 2020). It is relevant to mention that several cases have been reported that showed negative results in the respiratory tract, but still showed positive results in the stool samples (Hu et al., 2020).

It could be possible that fecal-oral transmission is another unexplored route of transmission. On the other hand, to date there is no evidence on the identification of intrauterine infection or mother-to-child transmission (Chen et al., 2020). It is essential to mention that people of all ages are generally susceptible, however the bulk of patients are concentrated in the group of 30 to 79 years, which represents 86.6%.

Patients with underlying diseases are more susceptible (Yuan et al., 2020), compared to men, women not only have fewer symptoms, but also have a longer incubation period.

Therefore, differential controls should be adopted as soon as possible. The incubation period for the virus is around 6.4 days (ranges from 0 to 24 days) (Wu et al., 2020).

Role of the ACE2 receptor in COVID-19 infection

We used three different databases for analyses, protein expression and localization. The human angiotensin-converting enzyme 2 (ACE2) is a zinc metallopeptidase containing 805 amino acids, the gene has been mapped to the X chromosome (Xp22) and it has 82% of identity and 85.1 of similarity with mice [www.genecards.org] (Stelzer et al., 2016). In mice, ACE2 is expressed in the kidney, lung, brain, heart, vasculature, and other organs [www.nextprot.org, ID: NX_Q9BYF1] (Zahn-Zabal et al., 2020). Relative to cell localization,

ACE2 expression has been observed in brush border membrane, cell surface, cytoplasm, extracellular exosome and extracellular space, membrane raft and others. The subcellular localization of the protein was retrieved from the COMPARTMENTS database [compartments.jensenlab.org, ID: ENSP00000389326] (Binder et al., 2014). ACE2 biological function and expression are different depending on the organism, tissue, and mainly are related to age and sex. In kidney has shown a peak on post-natal period and a decrease in adulthood, while in lung, brain and heart has a peak on adulthood (Song et al., 2012; Xudong et al., 2020), this could be the case for human as well. Animal models will be critical for development of medical countermeasures to the COVID-19 pandemic, although SARS coronaviruses are inefficient at infecting mice due to structural differences between mouse ACE2 and human ACE2, receptor crucial for virus entry and replication in humans. Laboratory mice infected with mouse-adapted strains of SARS-CoV and MERS-CoV have helped us in our understanding of viral pathogenesis and intervention strategies. Several animal models for SARS-CoV-2 have been reported, with varying degrees of viral replication and clinical disease (Le Bras, 2020; Sun et al., 2020).

In addition to be the receptor for several human coronaviruses, including SARS-CoV-2; ACE2, has enzymatic activity through its two domains: N-terminal and C-terminal. Among its molecular functions are carboxypeptidase activity, dipeptidyl-peptidase activity, endopeptidase activity, exopeptidase activity, metallopeptidase activity, zinc ion and protein binding. It also possess biological functions such as angiotensin maturation, positive regulation of amino acid transport, positive regulation of cardiac muscle contraction, positive regulation of gap junction assembly, positive regulation of reactive oxygen species metabolic process, receptor biosynthetic process, regulation of cell population proliferation, regulation of cytokine production, regulation of inflammatory response, tryptophan transport and viral entry into host cell [neXtProt ID: NX_Q9BYF1]. Thus, inhibition of this receptor is not a viable therapeutic option, since it could further affect the availability of ACE2 to carry out the mentioned functions. It is also one of the strengths of SARS-CoV-2, when using ACE2 as a binding and entry agent to the host cell it disables the other mechanisms, decreasing the ability of the immune modulating tissue to respond by increasing the oxidative stress, inflammation and apoptosis. This proposed interaction is based on the pathway of the angiotensin II, which its binding to the AT1 receptor, leads to cellular damage through the effects before-mentioned that cause neurodegeneration (Fig. 1) (Abiodun and

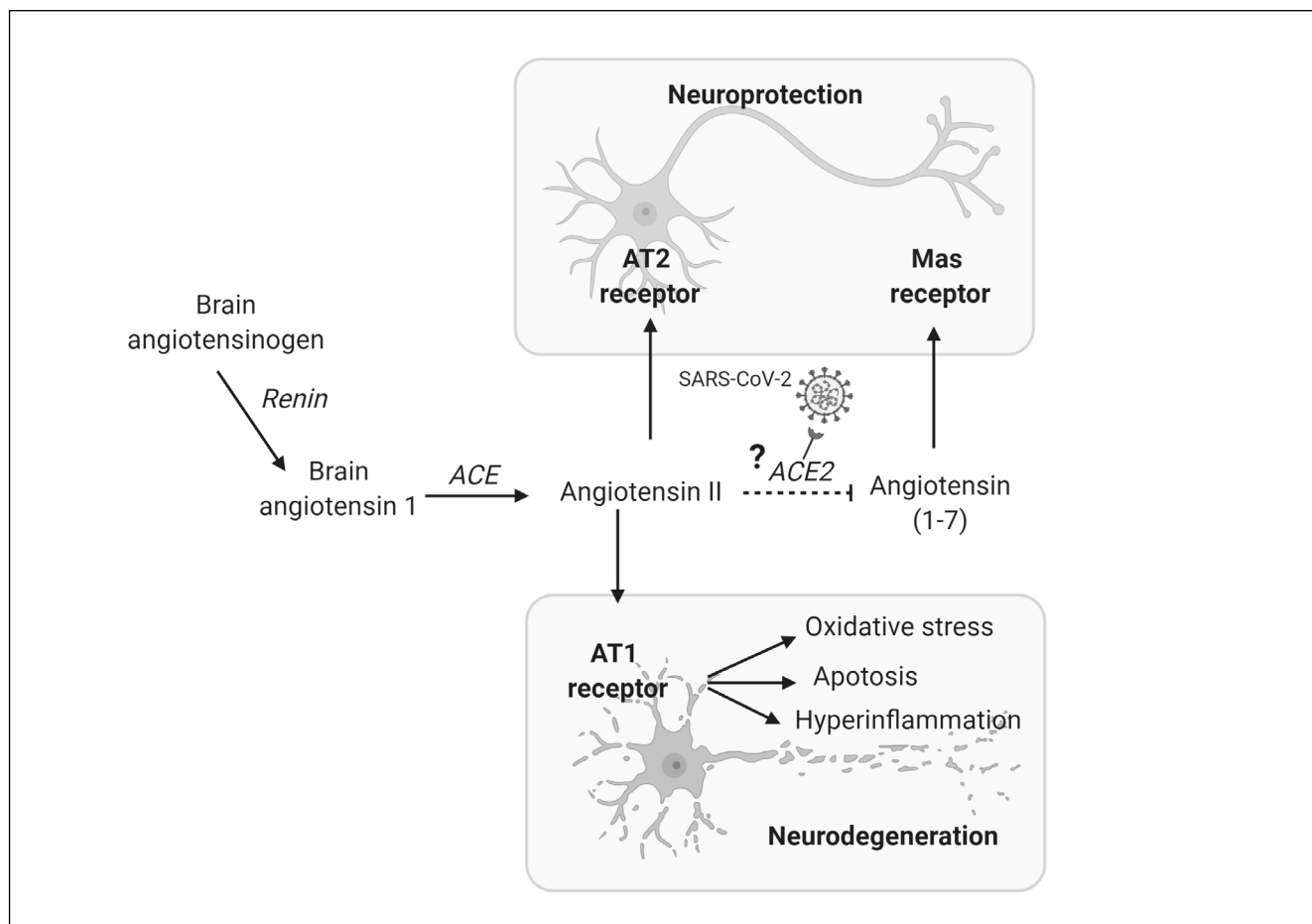


Fig. 1. Putative pathway between indirect SARS-CoV-2 nervous system damage through the brain renin-angiotensin system. ACE2 (angiotensin-converting enzyme II) possibly being blocked by SARS-CoV-2 leads to an inhibition of the ACE2/Ang 1-7 pathway that regulates mechanisms related to neuroprotection through the MAS receptor. Additionally, the AT1 pathway could be activated, which is related to hyperinflammation, oxidative stress and increased apoptosis, which ultimately would lead to neurodegeneration.

Ola, 2020). Furthermore, it has been observed that people with lung damage by smoking and those who developed chronic obstructive pulmonary disease (COPD) had a high level of the enzyme angiotensin. Furthermore, ACE2 expression is also increased in lung cells by influenza virus and by interferon treatment. In summary, SARS-CoV-2 triggers the increase in the expression of its own receptor with greater infectivity (Leung et al., 2020).

ACE2 in brain expression and activity

The viral genome of SARS-CoV-2 has been detected and sequenced in cerebrospinal fluid, the authors by means of deep sequenced using the MinION platform from Oxford Nanopore technology, reported a 99.74–100% similarity between the patient virus and worldwide sequences (Domingues et al., 2020). Viruses can reach the central nervous system (CNS) through he-

matogenous or neural propagation and nerve dissemination is possible by the polarization of neurons, this property gives them the ability to receive and transfer information. Nervous system expression of ACE2 has been widely described in mice (Table I).

This transport can be retrograde or anterograde and is facilitated by proteins called dynein and kinesin, which can be targets of viruses. Table II describes the anatomical sites where expression of ACE2 in CNS has been shown, and its possible relationship with signs and symptoms that patients show. Helms (2020) described that critical patients with COVID-19 present encephalopathy, confusion, and corticospinal tract signs inclusive, a few cases presented acute ischemic strokes. It is important to mention that different risk factors can increase infection of the nervous system, such as smoking (Kabbani et al., 2020). It has also been postulated that viral damage to the respiratory center in the brain can increase the respiratory problem (Conde et al., 2020).

Table I. Nervous system expression of ACE2 has been widely described in mice.

Ace2 gene expression data in CNS of mouse (Mouse Genome Informatics)		
Structure	Sex	Strain
Brain	Male	CD1, C57BL/6
Cerebral hemisphere	Female, male	CD1
Cerebellum	Female, male	CD1, C57BL/6
Cerebral cortex	Female	C57BL/6
Dorsal raphe nucleus	–	C57BL/6, CAST/Eij
Visual cortex	Male	CD1, DBA/2J, C57BL/6
Telencephalon	Male	C57BL/6
Hypothalamus	Female, male	Idaho-derived wild mouse
Dental gyrus	Male	C57BL/6
Hippocampus	–	(DBA/2 x C57BL/6J) F1
Corpus striatum	Male	C57BL/6, WSB/Eij
Olfactory bulb	Male	C57BL/6
Sciatic nerve	–	–
Prefrontal cortex	Female, male	C57BL/6
Preoptic area	Female, male	C57BL/6, CAST/Eij
Suprachiasmatic nucleus	–	C57BL/6
Arcuate nucleus	Female	(DBA/2 x C57BL/6J) F1
Thalamus	Female	C57BL/6

Table II. Ace2 gene expression data in human and its possible relation to COVID-19 signs and symptoms of neurological damage.

Ace2 gene expression data in human and its possible relation to COVID-19 signs and symptoms of neurological damage				
	Data source			Possible signs, symptoms and disease
Olfactory region	A			Anosmia, hyposmia
Cerebral cortex	A		C	Alterations in cognitive function (Grasby et al., 2020)
Hippocampal formation	A	B		Alterations in memory function (Steardo et al., 2020)
Amygdala	A			Alterations in olfactory tract (Swanson et al., 2015)
Basal ganglia		B	C	Hypokinetic disorders (Albin et al., 1989)
Hypothalamus		B		Hormonal disorder (Halmos et al., 2020)
Thalamus	A			Alterations in nociceptive pathway (Halmos et al., 2020)
Midbrain	A	B	C	Hypokinetic disorders (Bissonette et al., 2016)
Ponds and medulla	A		C	Respiratory dysfunction (Halmos et al., 2020)
Cerebellum	A		C	Ataxia (Shaikh et al., 2020)
Spinal cord		B	C	Ataxia (Shaikh et al., 2020)
Pituitary gland		B		Hormonal disorder (Halmos et al., 2020)

A – Consensus Human Brain dataset; B – GTEx Human brain RNA-Seq dataset; C – FANTOM5 Human brain CAGE dataset.

Infection of the CNS not only represents direct cellular damage by the virus, but also activates an exacerbated inflammatory response and significant oxidative damage, in addition to the fact that the virus can disable the neuroprotective enzyme capacity of ACE2 (Alenina et al., 2019) as represented in Fig. 2. In this regard, a significant change in ACE2/Ang 1-7 regulation as a neuroprotective mechanism may probably occur and may lead to the onset of a long-term neurodegeneration process in those patients with severe disease who are recovering. Therefore, it is of the outmost importance to continue studying the acute and chronic impact of COVID-19 on the nervous system.

As a consequence of this damage at the cellular level, evidence of damage can be found in animal studies, mainly in the hippocampus, an area of the brain that plays an important role in memory and spatial navigation. This vulnerability is seen not only in the context of a coronavirus infection, but also in other respiratory infections. Experiments with mice infected with the influenza virus revealed that morphological and functional changes occurred in the hippocampus of these

animals. Such changes are associated with impaired long-term spatial memory. It will also be necessary to determine if these brain changes caused by COVID-19 could accelerate the development of other pathologies, such as Alzheimer's disease, which is characterized precisely by causing damage to the hippocampus and deterioration of spatial memory (Sommer and Bakker 2020; Szcześniak et al., 2020).

Ventilated patients are known to be the most affected. Severe acute respiratory syndrome, which occurs in the most severe cases of COVID-19, sometimes cannot be avoided because mechanical ventilation is required to help patients breathe. This is another cause for concern because more than 70% of hospitalized patients whose condition requires mechanical ventilation, due to some other respiratory pathology, suffer from cognitive damage, mainly their ability to concentrate, their memory and their verbal fluency, and this even up to a year after being discharged (Busani et al., 2020; Sommer and Bakker, 2020).

Furthermore, it has been suggested that certain brain disorders (especially brain atrophy) associated

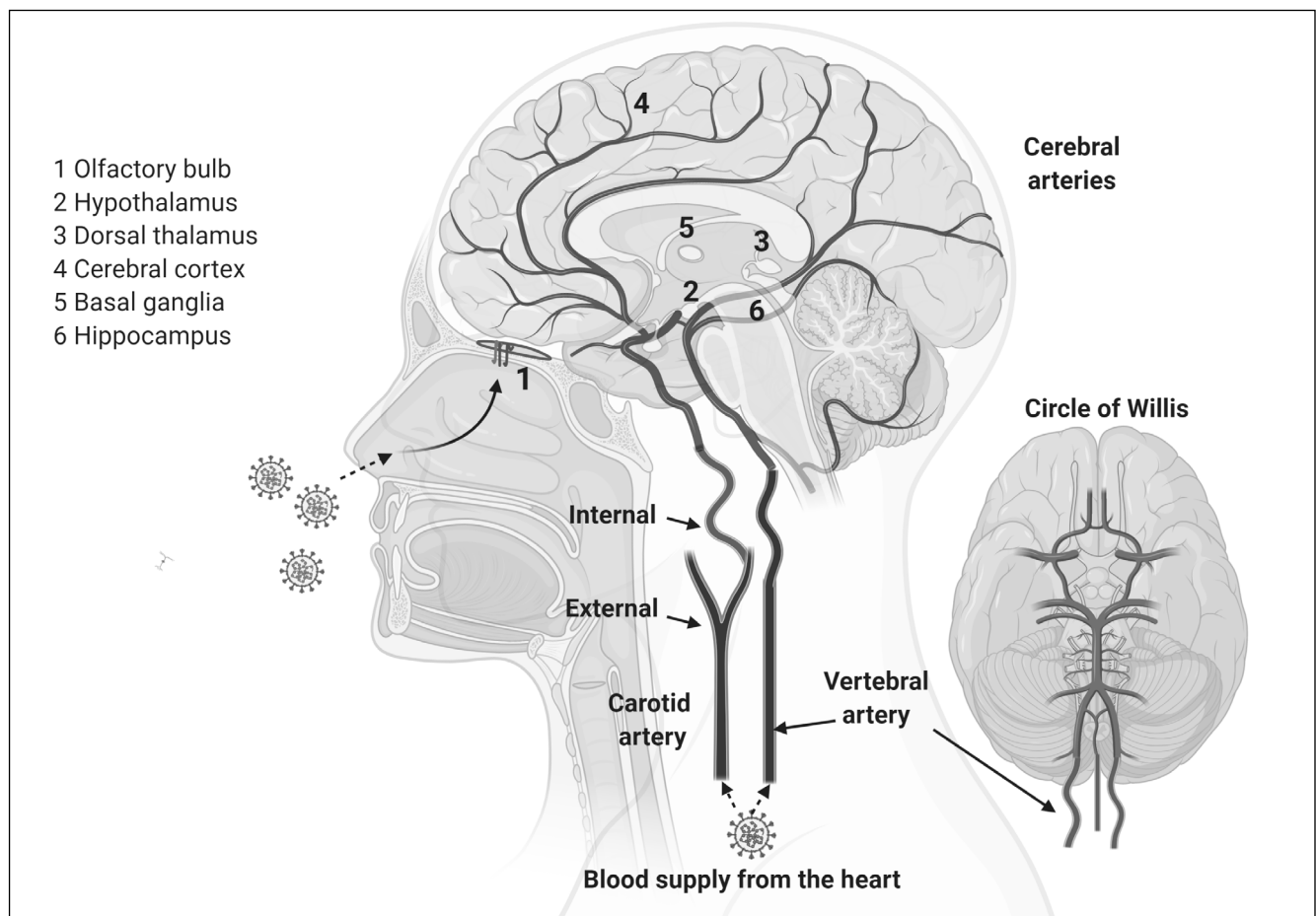


Fig. 2. Neuroprotective activity of the ACE2 enzyme and its relationship with neuronal damage in patients with COVID-19.

with attention problems, verbal memory, and executive functions (logic, planning, reasoning, etc.) that affect patients with severe acute respiratory syndrome, could be due to a lack of oxygen (hypoxemia) produced before proceeding to ventilation (Assaf et al., 2020; Wan et al., 2020; Alexopoulos et al., 2020).

As a consequence of the COVID-19 pandemic, an increase of unprecedented magnitude of psychiatric disorders in the general population is expected, due to the trauma caused by this disease in the CNS. However, it cannot be ruled out that some of these cases could be directly caused by the viral infection, which would have been responsible for the brain damage, and not only by environmental factors such as the climate of distress in which we lived for several months (Pattni et al., 2020; Rogers et al., 2020).

Possible mechanism of neurological damage

Viral infections can spread to neighbor tissues, where they can cause more serious damage due to virus replication or the innate immune reaction being overactivated (Koyuncu et al., 2013). Acute infection of the CNS does not have an apparent selective advantage for the host or the pathogen. However, a zoonotic infection, which are often minimally pathogenic in their natural hosts, can be highly virulent and neuroinvasive in human hosts (Al-Obaidi et al., 2018). The proper functioning of the brain partially depends on endothelial cells in conjunction with astrocytes and microglia; innate immune cells of the CNS that produce discriminatory immune responses to different phenotypes of viral infections (Li et al., 2004; Klein et al., 2017; Michalicova et al., 2017). Human respiratory syncytial virus (hRSV), influenza virus (IV), human metapneumovirus (hMPV), and coronavirus (CoV) are the most common ones that affect the susceptible population (Al-Obaidi et al., 2018). CoVs are a group of viruses that have been shown to have neurotrophic and neuroinvasive characteristics and can complicate the disease associated with their infection. CoV RNA has been detected in the CNS of patients with many neurological diseases. Coronaviruses are animal and human pathogens that can cause lethal zoonotic infections such as SARS and MERS. They have plus-strand polycistronic RNA genomes and belong to the order Nidovirales, a diverse group of viruses for which a common ancestry was inferred from the common principles underlying the organization and expression of their genome, and from the conservation of a series of core replicase domains, including key enzymes that synthesize RNA (Snijder et al., 2016; Kim et al., 2017).

The first case of SARS-CoV infection with neurological manifestations was reported in 2003 in a 59-year-old woman (Bohmwald et al., 2018). Recently, a study reported neurological manifestations in the current COVID-19 outbreak that involved 214 patients, of whom 78 (36.4%) patients had neurological manifestations (Baig et al., 2020). To access the CNS, respiratory viruses can enter through the hematogenous or neuronal retrograde pathway. In the former, the virus infects neurons in the periphery and uses the axonal transport machinery to access the CNS. In the latter, the virus uses the bloodstream to carry the infection through the blood-brain barrier (BBB) into the cerebrospinal fluid (Bohmwald et al., 2018; Desforges et al., 2019). Pathogens can cross the BBB by paracellular, transcellular, and/or “Trojan horse” mechanism (Bohmwald et al., 2018).

The olfactory system provides a single entrance portal and is directly accessible to the CNS from the periphery, it is literally one synapse away from the environment. The olfactory nerve, which belongs to the peripheral nervous system (PNS), innervates the olfactory epithelium, and ends in the olfactory bulb in the CNS. Thus, by trans-synaptic spread, a virus can reach other parts of the brain (Mori, 2015). The olfactory epithelium is well protected from the most common mucus infections, and the presence of various pathogen recognition receptor systems. However, in animal models, the olfactory portal can be used by some viruses (Li et al., 2004; Koyuncu et al., 2013). The olfactory system forms direct connections with the frontal cortex without thalamic retransmission, while other sensory pathways of the visual, auditory, and somatosensory modalities constantly pass through the thalamus. The PR8 strain of influenza A (H1N1) virus, a non-neurotropic virus, can also infect olfactory sheath cells, as well as microglia/macrophages along olfactory nerve fibers (Desforges et al., 2019). Likewise, it was shown that both HCoV-OC43 and SARS-CoV-2 can infect the respiratory tract in mice and are neuroinvasive; the virus spread to various regions of the brain and brainstem before it reached the spinal cord (Desforges et al., 2019). Furthermore, the route of entry through the blood supply is through secondary lymphoid tissues, viruses are often released into the bloodstream, causing a systemic infection a process called viremia (Bohmwald et al., 2018). Some viruses directly infect vascular endothelial cells, allowing direct passage through the BBB into the CNS (Desforges et al., 2019) (Fig. 3).

Infected hematopoietic cells are also used as “Trojan horses” to transport the virus to the CNS through the blood supply (Swanson et al., 2015). It was recently reported that in patients affected by SARS-CoV-2, the

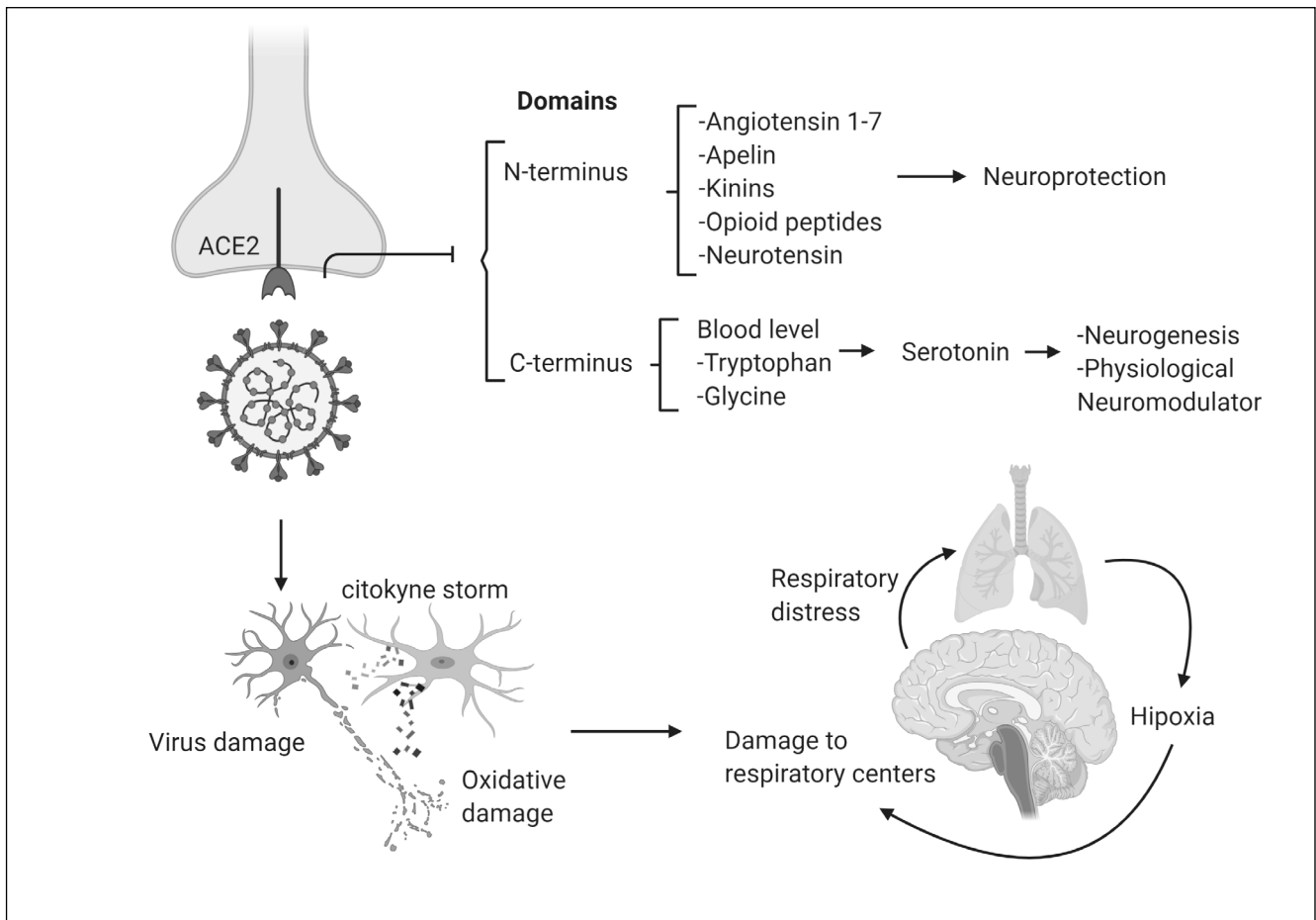


Fig. 3. Route of entry of the virus to the brain and its relation to damage to different structures.

spread of the virus, in the systemic circulation during an early or later phase of infection, could lead to brain compromise. It is proposed that the slow movement of blood within the microcirculation could be one of the factors that may facilitate the interaction of the COVID-19 virus with ACE2 expressed in the capillary endothelium (Baig et al., 2020). ACE2, which is found in the lower respiratory tract of humans, is present in the nervous system and skeletal muscle (Guo et al., 2020; Mao et al., 2020). Immune receptors generally exist in cell membranes and bind to factors like cytokines, resulting in an immune system response (Al-Obaidi et al., 2018). The brain expresses ACE2 receptors, it has been detected on both glial cells and neurons, SARS-CoV-2 interaction with ACE2 receptors expressed in neurons is proposed to be the first step in a viral budding cycle accompanied by neuronal damage without substantial inflammation as seen in cases of SARS-CoV-2 in the past (Baig et al., 2020). However, the SARS-CoV S protein can downregulate ACE2 and induce the removal of the catalytically active ectodomain ACE2, reduced ACE2 function can cause dysfunction of the renin-angioten-

sin system, increases inflammation and vascular permeability (Fu et al., 2020).

There is clinical and experimental evidence of the role of astrocytes and microglia as target cells in some human CoV variants. Furthermore, astrocytes and microglia have been shown to play an important role in neuroinflammation processes, responding to local inflammation of the CNS and imbalanced peripheral inflammation (Murta et al., 2020). SARS-CoV-2 also is neuro-invasive and can spread to the brain, causing a chronic immune imbalance, which underlies possible long-term effects on synapses and neuropsychiatric disorders (Wu and Tang, 2020; Li et al., 2020). Furthermore, accumulating evidence has shown that neuroglia is the target of several neurotropic viruses that severely affect its function. Glial cell dysfunctions have been associated with several neuroinflammatory diseases. It could be plausible that SARS-CoV-2 has a primary effect on these cells in addition to a secondary effect of neuronal damage. Taking into account the mechanism of action of other neurotropic viruses and neurodegenerative diseases where the participation of the glia is

relevant, it is likely that SARS-CoV-2 has direct and indirect effects on the glia and that it plays an important role in COVID-19. Whether glial activation is beneficial or harmful to the brain in COVID-19 pathology is still a subject of extensive research (Vargas et al., 2020; Mehta et al., 2020; Helms et al., 2020).

Recent clinical studies have described the role of neurofilament light chain protein (NfL) (intra-axonal neuronal injury marker) and glial fibrillary acid protein (GFAP) (astrocytic activation/injury marker) as biomarkers. NfL and GFAP have been described to be present when there is a CNS injury by analyzing the CSF. GFAP is an intermediate filament, highly expressed in astrocytes, and serves as a marker of astrocytic activation/injury. NfL is an intra-axonal structural protein and a neuronal injury biomarker, Kanberg et al. (2020) found that astrocytic activation/injury (GFAP measurements) can be a common feature in moderate and severe stages of COVID-19, while neuronal injury (NfL) occurs later in the disease process and primarily in patients with severe disease. They hypothesize that astrocytic activation/injury is a first response to CNS aggression and that the increase in plasma NfL reflects a progression to neuronal injury in severe cases. Furthermore, biomarkers may be a good indicator of SARS-CoV-2 infection in the CNS, and could allow understanding its underlying role in CNS inflammation. The results in patients with COVID-19 and neurological symptoms suggest an unusual pattern of marked CSF inflammation in which soluble markers increased, but the response of white blood cells and other immunological features typical of viral CNS infections were absent. This result may be due to the fact that the measurement in CSF is more complicated than in serum, in addition to the fact that the patient sample was small. Although the hypothesis remains that they are useful for the diagnosis of CNS pathobiology derived from SARS-CoV-2 infection (Eden et al., 2020).

On the other hand, recent studies have proposed that astrocytes and microglia are not viral hosts. Astrocytes and microglia are not primary targets of viral infection, but respond to pro-inflammatory signals from endothelial cells, macrophages and neurons. In such a case, astrocytes and microglia can turn to a pro-inflammatory phenotype that would further spread neuroinflammation (Murta et al., 2020).

Additionally, laboratory findings on COVID-19 indicate the involvement of cytokines. Lavi and Cong (2020) demonstrated that an experimental murine coronavirus (MHV-A59) can be transmitted to the brain by intranasal or intracerebral exposure and that neurovirulence is mediated by cytokine secretion. They conclude that cytokine secretion by type I astrocytes and microglia, as part of the brain's innate and glyphatic

immune system, contribute to the pathogenesis of an encephalitic coronavirus infection. Thus it indicates the rationale for anti-cytokine therapies for COVID-19 (Lavi and Cong, 2020).

The “cytokine storm” can cause devastating effects on the brain resulting in meningitis, encephalitis, meningoencephalitis, or even death. These effects are the result of pathophysiological events that affect the function of the BBB, brain metabolism, oxygen consumption, and blood flow. (Al-Obaidi et al., 2018; Klein et al., 2017). Patients infected with the H5N1 virus die, not from robust replication of the virus, but from acute respiratory distress syndrome (ARDS) triggered by the “cytokine storm” (Koyuncu et al., 2013). It is suggested that the neuropathological effects of MERS-CoV infections are the result of immune-mediated processes, either directly by viral invasion or by molecular changes arising from the systemic inflammatory response syndrome (Kim et al., 2017). Very recent studies propose that the secretion of the cytokines involved in the cytokine storm as well as substance P (SP) intervenes in the TRPV1 ion channels, which can be activated by external aggressors such as a viral infection. It is expected that it is established a neuroimmune communication with the purpose of protecting the individual and that, paradoxically, the severity would be increased in patients with COVID-19 (Aguirre-Siancas et al., 2020).

Likewise, the infiltration of immune cells and the production of cytokines in the CNS of mice were observed after HCoV-OC43 infection (Desforages et al., 2019). Finally, SARS-CoV-2 infection also causes increased secretion of IL-1b, IFN-c, IP-10, MCP-1, IL-4, and IL-10 (Huang et al., 2020). Recently it was reported that 36.4% (78/214) of patients with COVID-19 develop neurological symptoms, such as headache, altered consciousness, and paresthesia (Wu et al., 2020). It is important to mention that patients infected with severe COVID-19 have been shown to be more likely to develop neurological symptoms, especially acute cerebrovascular disease, conscious disorder and muscle injury (Mao et al., 2020). In addition, it is relevant to mention that several health centers have shown an abnormal increase in patients admitted with Guillain-Barré syndrome, showing a much higher age prevalence (mean 60 years) than cases of this pre-pandemic syndrome (mean 40 years) (Trujillo et al., 2020; Baig, 2020).

Based on what has been previously described, we can argue that the cellular damage caused in the brain by COVID-19 produces several undesirable effects such as, delirium or encephalopathy, sometimes paired with psychosis and memory alteration and encephalitis. In turn, inflammatory lesions, like acute disseminated encephalomyelitis are shown, along with the effects of low oxygen levels in the brain, plus, blood clots

that could lead to strokes even in younger patients, and eventually potential damage to the body's nerves, causing pain and numbness. In addition to these alterations, ischemic lesions have also been found. Some of these patients have risk factors for stroke due to comorbidities such as high blood pressure, diabetes, or obesity. This appears to be because the blood thickens rapidly with COVID-19, and in these patients, multiple blood clots have occurred in the arteries that could carry blood to the brain, even in patients already on anticoagulants. In others without comorbidities, there could be cerebral hemorrhages due to weakening of the blood vessels, perhaps inflamed by the effects of the virus (Fierini et al., 2020; Maulik et al., 2020; Steardo L Jr. et al., 2020; Velayudhan et al., 2020). Several studies have found that the occurrence of strokes in patients with COVID-19 infection is rare, but it is still present as an important prognostic marker and indicator of severity. This suggests that ischemic stroke can occur early in the course of the disease and can also affect patients in the younger age groups without comorbidities, causing occlusion of the great vessels and exhibiting a thromboinflammatory vascular picture. Since many COVID-19 patients share common traditional risk factors for stroke, clinicians need to be vigilant in the future for an increase in the number of strokes in COVID-19 patients as the pandemic continues and take appropriate preventive measures (Lee et al., 2020; Wang et al., 2020; Rameez et al., 2020).

CONCLUSION

There is increasing evidence that the nervous tissue is susceptible to being infected by SARS-CoV-2. The affected structures will depend on the level of expression of ACE2, on the availability of the structure to be infected, either by the nasal route or by blood circulation. The host's response depending on its general state of health, the inflammatory and oxidative response at the nervous tissue level and the ability to compensate for the neuroprotective decrease in ACE2 partially inactivated by the virus.

It is important to note that the virus has the potential to infect the brain directly and indirectly. However, most of the prevalent symptoms seen in patients in remission appear to be consequences of the viral infection; oxidative stress, inflammation and apoptosis, in the brain rather than the effects of the viral infection itself. Our immune system can adequately fight the virus, but it can start attacking our own cells, including neurons, glia, blood-brain barrier, and nerves. This may be through the actions of immune cells and antibodies through an inflammatory

mechanism known as “cytokine storm”, which causes a sharp accelerated cognitive decline beyond what is expected in patients who have not had previous neurological disorders. To date, the patterns of these effects appear similar worldwide. Some of these changes are deadly and will have long-term consequences for those who survive.

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