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SARS-CoV-2, ACE2, panendothelitis and viral neuroinvasion. Systemic consequences

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Abstract

The emergence of a novel, highly contagious coronavirus led to an increasing number of pneumonia cases in the Wuhan region which were associated with severe acute respiratory syndromes and subsequently led to the beginning of the coronavirus disease 2019 (COVID-19) pandemic. However, COVID-19 manifests not only as a pulmonary disease but also as a systemic disease, both during the viremia and cytokine storm phase. The multiple systemic manifestations of infections with SARS-CoV-2 are hereby explained by both direct viral effects and the widespread distribution of the angiotensin-converting enzyme 2 (ACE-2) receptor, which acts as a viral cellular gateway. This review focuses on the link between SARS-CoV-2 and the ACE-2 receptor, which allows the development of systemic panendothelitis and underlines viral neuroinvasion mechanisms leading to the potential neurological complications in COVID-19 patients.

Keywords: SARS-Cov-2, panendothelitis, viral neuroinvasion.

It is known that at the onset of the Wuhan infections with SARS-CoV-2 and the identification of a novel virus at the beginning of 2019, the "natural" emergence of a coronavirus that induces COVID-19 disease was taken into consideration, which was defined by a severe acute respiratory syndrome.

The origin of the virus was considered to be natural, and it was linked to the SARS-CoV-1 virus as they demonstrated 80% genome similarity. However, the SARS-CoV-2 genome seems to be much more closely linked to that of the bat coronavirus, revealing 96% genomic identity. Both coronaviruses share the same angiotensin-converting enzyme 2 (ACE-2) receptor, which mediates cell-entry. The widespread vascular and tissular distribution of the ACE-2 receptor allows an accurate understanding and interpretation of not only the pathogenic respiratory consequences but also the multisystemic ones [1, 2]. The link between the viral spike (S) protein and the ACE-2 receptor is based on hydrogen-bonds and electrostatic interactions. However, hydrophobic interactions which may influence viral affinity for the ACE-2 receptor have been identified.

Both SARS-CoV and SARS-CoV-2 target the same regions of the ACE-2 receptor, yet they differ by dynamic and energetic types of interactions. One significant difference is the stable bond between a SARS-CoV-2 protein S lysine and one aspartic acid within the ACE-2 structure and three additional stable hydrogen bonds, which are not observed in the case of SARS-CoV. It has been previously emphasized that the stable interactions between the virus and the host receptor are essential for the process of cell-entry [3]. This is why these stable interactions

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may suggest new approaches in the design of the antiviral agents to target and destroy these interfaces.

The first analysis of the coronavirus pathogenic behavior, which was performed almost 15 years ago, emphasized that the first step into understanding its pathogeny is the clarification of the ACE-2 tissular distribution [4] and the affinity of SARS-CoV-2 towards its receptor.

The origin of SARS-CoV-2, whether natural evolution or obtained by genetic engineering, remains debatable and will require further data for clarification. What is certain is that the intermediary host (before the evolutionary jump to the human host), the viral sequencing of the initial cases, and the mechanisms of natural selection of SARS-CoV-2 are of essential importance [5–7].

Taking into account their importance, we sought to summarise the genetic and structural SARS-CoV-2 characteristics. Certain aforementioned and cited authors have emitted the concept that the "chimeric structure of SARS-CoV-2 and the furin cleavage may be a result of genetic manipulation".

The following genomic characteristics of SARS-CoV-2 have been considered notable [5]. Two significant genetic differences have been distinguished in structural and biochemical studies of the alfa and beta coronaviruses:

- The interaction between SARS-CoV-2 and human ACE-2 has been optimized; the affinity of SARS-CoV-2 towards ACE-2 is significantly greater than that of SARS-CoV [3];
- There is a furin cleavage site within the binding domain of SARS-CoV-2 spike glycoprotein between S1 and S2, which allows attachment of three O-glycans.

The host-receptor binding domain of the spike protein exhibits considerable variability and susceptibility for mutations and relies on a critical structure of 6 amino acids. The affinity for human tissular ACE-2 is regarded by many authors as a result of natural selection. Andersen *et al.* have proposed three alternative scenarios [5]:

- The first scenario supposes that natural selection may have occurred in an animal host (which may be represented by bats) before zoonotic transfer. The bat-infecting coronavirus shows 96% genetic similarity. However, the binding spike domain exhibits differences that suggest low affinity of human ACE-2. The pangolin has also been regarded as a possible host before zoonotic transfer as there is important similarity (even in the domain-binding aminoacids) between pangolin-infecting coronaviruses and SARS-CoV2;
- The second scenario considers that natural selection occurred after zoonotic transfer. This means that after the transfer to humans from the initial animal hosts, there is undetected human-to-human transmission which allows for viral adaptive changes. Once adopted, this may generate the pandemic phenomena. This may be comparable to the repeated jump of the Middle East respiratory syndrome coronavirus (MERS-CoV) from dromedaries to humans, which does not lead to adaptive processes that would withstand transmissibility. Serological studies are to clarify the extent of the pre-pandemic human exposure to SARS-CoV-2;
- The third scenario is based on the temporal selection in animal models or passage-dependent selection, which may admit the laboratory-leaked hypothesis. It has already experimentally been shown that viral mutations are possible during cell culture or animal passage. The authors emphasize the following: although current evidence shows that SARS-CoV-2 is not a genetically manipulated virus, it is currently impossible to test other theories of its origin; since particular characteristics of SARS-CoV-2 have been described (including the binding-domain optimization and the cleavage site) in related natural coronaviruses, we do not believe that a laboratory scenario is possible.

Ang II converting enzyme (ACE2), physiological functions, and pathogenic implications as the SARS-CoV-2 receptor

The degradation product of Ang II under the catalytic activity of ACE-2 is Ang (1–7) (which is different from the ACE pathway, which converts Ang I to Ang II with vasoconstriction, proinflammatory, and profibrotic effects). Ang (1–7) induces vasodilation, antiproliferative and apoptosis effects which are generally in opposition with those of Ang II. The complex interactions in the renin-angiotensin-aldosterone system (RAAS) have already been described. ACE-2 catalyzes the conversion of Ang I to Ang (1–9), of Ang II to Ang (1–7), which are essential stages of the complex control of RAAS and the cardiocirculatory, hydroelectrolytic and its multiple other effects [8]. ACE-2 has been identified in the year 2000 by Donoghue *et al.* [9]; multiple papers have been directed towards the description of its genesis, functions, involvement in cardio-circulatory control and roles in renal physiology, diabetes, pulmonary protection and finally, the role of SARS-CoV's and SARS-CoV-2's receptor [4, 10].

ACE-2 is widespread in multiple tissues (heart, kidney, testicles, liver, intestinal tract, brain, and widely in the vascular endothelium). Research concerns and efforts regarding ACE-2 have further intensified since the discovery of its role as the SARS-CoV-2 receptor. ACE is distributed on the

cell surface and is not easily internalized. The cell surface expression of ACE-2 reduces through internalization after interaction with SARS-CoV-2. Proteolytic shedding of the extracellular enzymatic domain is another mechanism of surface expression and leads to detectable plasmatic levels [4].

The widespread tissular distribution of ACE-2, including endothelial and microcirculation presence, explains the multiorgan involvement in COVID-19 (most prominent through lung involvement and vascular thrombosis, which frequently are the mortality causes). Hamming *et al.* have emphasized that understanding ACE-2 distribution is crucial, as it acts as the functional receptor for coronaviruses [4].

There is a clear difference of receptor activity that correlates with ACE-2 distribution, being significantly more pronounced in the lungs of males versus females. Consequently, even though not reaching statistical significance, the SARS-CoV-2 infection is more frequent in males (58.1%) versus females (41.9%), as shown by data derived from 1099 patients [10, 11]. Furthermore, age is considered to add vulnerability to COVID-19, as elders exhibit more severe disease and age correlates with an unfavorable prognosis. Pediatric patients usually manifest asymptomatic, mild, or moderate forms in 90% of cases. Essentially, the lower expression of ACE-2 may be correlated with the lower susceptibility of children to SARS-CoV-2 infection. In this way, children are susceptible to the disease but develop less severe forms in comparison to adults, and there seem to be no gender-related differences in susceptibility at a young age.

Tissular ACE-2 expression is correlated with different lifestyles. COVID-19 is more severe in smokers. It is known that nicotine may suppress ACE-2/Ang (1–7) Mas receptor activity and increases the expression of the ACE/Ang II/AT1 receptor with the subsequent consequences, which we have already described. Also, ACE-2 levels increase in diets rich in sodium chloride and may be correlated to the arterial hypertension prevalence. Glucose-rich diets may also increase ACE expression and lower the ACE-2 values, which leads to an unbalance between the two components (ACE/ACE-2) in the cardiovascular system.

Hypoxia-inducing lung disease (e.g., Chronic obstructive pulmonary disease) initially leads to a rise in ACE-2 expression in smooth muscles of the pulmonary artery, which is later followed by the inhibition of ACE-2 and the expression of ACE. Patients suffering from arterial hypertension or pulmonary hypertension have been identified to exhibit lower levels of ACE-2 in the lungs, blood vessels, kidneys, and brain. Similar aspects have been noted in experimental models of arterial hypertension [10]. Comorbidities such as coronary artery disease lead to increased risk of severe COVID-19 forms, and it is known that myocardial injury is a frequent complication of COVID-19. Cardiac complications aggravate and further deteriorate pulmonary function.

Interestingly, studies in diabetic patients have shown that ACE/ACE-2 levels positively correlate with systolic blood pressure, fasting blood sugar, serum creatinine and proteinuria. Essentially, COVID-19 disease has an unfavorable prognosis in diabetic patients, and the reason is linked to the mal-expression of ACE-2 [10].

Systemic panendothelitis

The reduction in ACE-2 expression leads to a predominance of Ang II effects by lowering the levels of its antagonist – Ang (1–7). The unbalance between the two components – Ang II, which activates the AT1 receptor (and being produced under the effect of ACE), versus Ang (1–7), which activates the Mas receptor (mediated by ACE-2).

SARS-CoV-2 cell entry is essentially based on the interaction between the endothelial ACE-2 and the alveolar pneumocytes.

Consequently, multiple phenomena occur: endothelial destruction, ACE-2 expression reduction and hypofunction (i.e., Ang (1–7) production from Ang II), destruction of type 1 and 2 pneumocytes and the alveolar-capillary membrane, leading to alveolar leakage of plasmatic proteins and formation of hyaline membranes; the subsequent relative increase in Ang II levels lead to AT1 activation which generates platelet aggregation, prostacyclin and NO-synthetase reduction with increase in vascular and microvascular thrombosis, mononuclear phagocytes activation and diffuse endothelial and alveolar inflammation. Altogether, every pathogenic link which increases the effect of Ang II and AT1 and reduction in Ang (1–7) will lead to pulmonary and systemic endothelial inflammation, which produces respiratory and multiorgan failure (in critical cases) [6, 10, 12, 13].

Is COVID-19 essentially a form of systemic endothelial dysfunction?

COVID-19 is a disease that primarily affects airways and lung parenchyma. In severe/critical cases, it may induce acute respiratory distress syndrome (ARDS) with respiratory failure, multiorgan failure with complex pathogenesis, including disseminated intravascular coagulation.

The European Society of Cardiology's recent position paper underlines that cardiovascular complications are common in COVID-19 in addition to the respiratory pathological processes [14].

A critical position is held by the endothelium, which is both a viral target and the main factor in inducing inflammatory and thrombotic effects by endothelial dysfunction, which leads to an unfavorable prognosis [14]. Moreover, the aforementioned group states that endothelial cellular dysfunction is actually a central characteristic of COVID-19 and has critical involvement in inflammation which initiates and coordinates cytokine dysfunction (storm), leading to ARDS and other cardiovascular dysfunctions. Prothrombotic status and disseminated intravascular coagulation are also clearly noted by the authors.

COVID-19 survivors have systemic immune activation mediated through cytotoxic CD8+ T-cells that destroy infected cells. CD4+ T cells are also involved and raise the levels of IL-4, IL-5, and IL-10, which is associated with mortality. Interestingly, the cytotoxic effect of CD8+ T cells in elders is severely limited [15]. Cytotoxic CD8+ T cells eliminate infected cells and have the central biological role of antiviral control. Moderate forms of COVID-19 involve a vigorous CD8+ T cell response. However, the cytotoxic capacities of T cells are not apparent in elders over 80 years old, which may explain the lower frequency of severe forms of COVID-19 in this age category.

As a consequence of endothelial dysfunction, procoagulant and prothrombotic phenomena are noted, as well as the reduction of antiaggregant prostacyclins and an increase of the proaggregant thromboxane caused by platelet activation.

As mentioned, ACE-2 is a key part of the renin-angiotensin-aldosterone system alongside ACE (Figure 1). Therefore, raising the risk of SARS-CoV-2 infection by increasing the levels of endothelial ACE-2 has been a matter of debate regarding certain antihypertensive molecules (ACE inhibitors of AT1 blockers).

Previous studies have not proven increased risk of disease or severity. The European Society of Cardiology and other counterparts have recommended continuing ACE inhibitors and AT1 blockers during the pandemic [16, 17]. Tissular lesions outside of the respiratory tract (i.e., heart, kidneys, liver, brain) are mediated by endothelial ACE-2 interactions [18–21]. Consequently, current evidence shows that SARS-CoV-2 infection of the endothelium leads

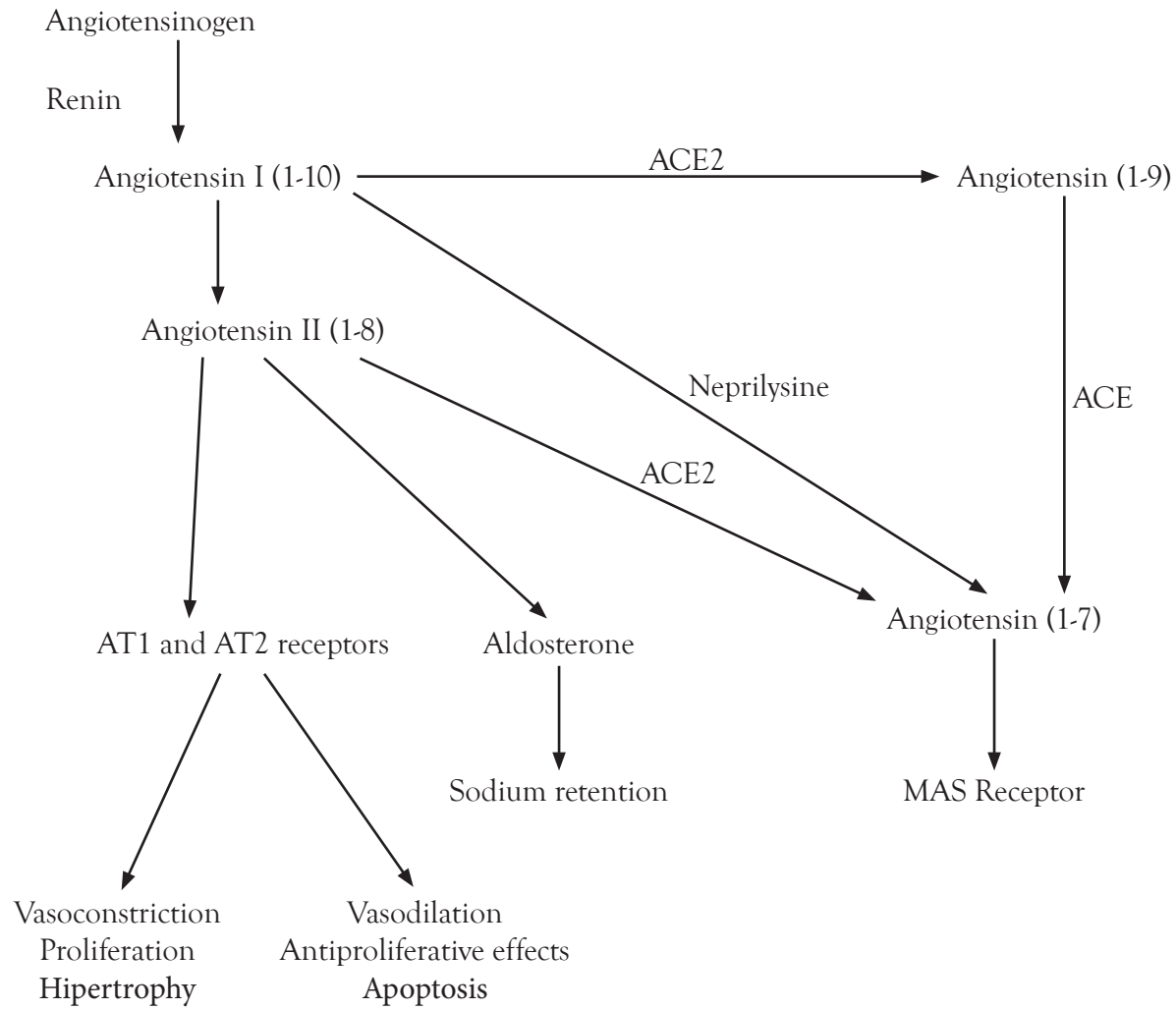

Figure 1. Roles of ACE2 within the renin-angiotensin-aldosterone system.

to direct lesions and cellular apoptosis, which promotes endothelial dysfunction. The endothelial dysfunction produced by SARS-CoV-2 resembles Kawasaki's disease (multisystemic vasculitis, more frequent in children, that targets the myocardium and coronary arteries for which a coronavirus-type RNA viral origin may be considered).

The role of pericytes has been recently discussed [14]. These are multifunctional mural cells present in the microcirculation, which have essential functions for endothelial integrity. It has been proven that ACE-2 is greatly expressed in pericytes in the myocardium, both in human and murine models. These cells have a low density in alveolar capillaries in COVID-19 pneumonia (probably mediated by apoptosis). In conclusion, pericytes seem to act as direct targets for SARS-CoV-2 and may have a crucial role in microvascular dysfunction and COVID-19 coagulopathy.

Viral neuroinvasion

It is known that anosmia and ageusia are specific signs of central nervous system (CNS) implication in COVID-19. It is debatable whether SARS-CoV-2 has the capacity of blood-brain barrier (BBB) penetration and if the neuropathology associated with COVID-19 is a direct consequence or is indirectly mediated by systemic dysfunctions.

In addition to the two aforementioned symptoms, headache, seizures, confusion, visual impairment, dizziness, nausea, emesis, hemiplegia, ataxia, stroke, and intracerebral hemorrhage have also been described [22]. SARS-CoV-2 neuroinvasion has been widely described throughout last year's publications [23–26]. Certain authors strongly highlight that the interaction between SARS-CoV-2 and ACE-2 receptor leads to tight junction dysfunction in the BBB, which ultimately leads to microglia neuroinvasion. Furthermore, the authors have emphasized the role of neuroinflammation and oxidative stress amplification, both leading to neuron death [24].

It is clearly not surprising that SARS-CoV-2 interacts with the ubiquitarian localized ACE-2 receptor at endothelial, neuronal, microglial levels and generates all the previously described pathogenic processes [6, 27]. Certain respiratory symptoms are also a direct consequence of SARS-CoV-2 CNS effects [28, 29]. The presence of SARS-CoV-2 RNAm within the cerebrospinal fluid (CSF) in patients with encephalitis suggests direct penetration of the BBB by the virus. However, an indirect consequence of SARS-CoV-2 infection is also considered, resulting from the cytokine storm affecting the CNS, without viral penetration of the BBB.

It has been previously investigated if the S1 protein of the ACE-2 binding viral domain can directly penetrate the CNS [22]. Rhea *et al.* have shown that S1 is able to cross the BBB in mice and produce neuro and endothelial invasion by intravenous or intranasal administration of the protein and have analyzed its inflammatory response. The authors consider that the widespread of the S1 protein within the mice CNS may account for complications such as encephalitis, respiratory-related neurological complications, and anosmia. Additionally, the authors have discussed that spike proteins or the virus may use multiple other receptors with less specific interactions. SARS-CoV-2's spike protein exhibits higher electrostatic affinity than that of SARS-CoV, and it is able to bond with a wider variety of receptors. This has already been shown in other viruses that are able to bond with other less specific receptors.

SARS-CoV is able to produce lethal infections after experimental intranasal administration or by accidental contamination. The virus subsequently advances to the respiratory system and further (including the CNS) through the circulatory system, and it is suggested that CNS-directed olfactory nerve passage is possible as it has been demonstrated in other viral infections. However, it seems that the primary gateway towards CNS infection is the BBB.

Consciousness loss has been described as a consequence of SARS-CoV-2 neuro-infections [29]. Viral infection in mice by nasal (olfactory epithelium) invasion may result in animal death [30, 31]. Circulatory viral dissemination or through the cribriform ethmoidal plate during initial infection appears to lead to CNS infection. Cerebral microcirculatory endothelial lesions may permit viral CNS invasion and neuronal ACE-2 viral bonding with leads to viral replication and neuronal lesions in the absence of significant inflammation [30]. These processes may lead to capillary rupture and cerebral bleeding [31].

Out of the seven types of coronaviruses, at least two are able to penetrate and reside within the CNS. Forty-eight percent of the studied patients have shown SARS-CoV-2 RNA extravascular presence within the CNS [32, 33]. Meinhardt *et al.* have described the complex results of 33 deceased COVID-19 patients during March-August 2020 [32]. Neurological manifestations consisted of loss of consciousness (5), intraventricular hemorrhage (2), headache (2), behavioral disorders (2) and acute cerebral ischemia (2). All 33 patients required mechanical ventilation, 9 of which had refused this procedure. Thirty-one of the included patients had positive RT-PCR results, while the remaining two exhibited highly suggestive symptoms of COVID-19.

The presence of intact viral particles and SARS-CoV-2 RNA within the olfactory epithelium was noted, as well as within the cerebral olfactory areas, which suggests that neuroinvasion may be possible via axonal pathways. The authors also state that the demonstration of CNS SARS-CoV-2 presence is difficult due to the low number of olfactory bulb neurons and the influence of the initial viral infecting

load. Moreover, viral presence has been noted in areas independent of the olfactory bulb (i.e., cerebellum). The capacity of invasion of the olfactory bulb may lead to the possibility of subsequent CNS-mediated dysfunction of respiratory and circulatory systems. Available data show that SARS-CoV-2 neuroinvasion may be produced at the neuronal – olfactory epithelium interface with trans-mucosal transport of the virus towards the CNS via the olfactory pathway, which may account for the neurological, behavioral and psychiatric symptoms. This is another pathogenic pathway by which SARS-CoV-2 may lead to death by dominant CNS implication and cerebral edema. The histopathological examination of CNS tissue of SARS-CoV-2 infected patients exhibited neuronal degeneration, necrosis, edema, microglial hyperplasia, and lymphocytic and monocytic vascular parietal infiltration. Certain studies have tried to summarize the neurological dysfunctions of COVID-19, and these have varied from Guillain–Barré syndrome to acute myelitis to hemorrhagic necrotizing encephalopathy [30, 34] Therefore, SARS-CoV-2 does not only affect the lung but also affects the CNS and leads to anosmia, ageusia, headaches, nausea and emesis in more than one-third of COVID-19 patients [23, 27, 32, 35].

A study that included 214 COVID-19 patients has shown that more than 36% had neurological symptoms, cerebrovascular dysfunction, loss of consciousness, or motor dysfunctions. 18% of patients exhibited major neurological dysfunction and required admission to the intensive care unit. Strokes have been described in 30–to 40-year-old patients [36]. Toxic encephalopathy associated with cerebral edema has been described in certain highly viraemic and hypoxic forms of COVID-19.

Although the mechanisms are yet to be fully clarified, multiple potential pathways that may explain the cerebrovascular and neurological dysfunctions encountered in COVID-19 have been mentioned. These mechanisms are also correlated with arterial hypertension induced by the interaction between SARS-CoV-2 and ACE-2, with a higher risk of hemorrhagic stroke. This is even more probable in patients already suffering from arterial hypertension. Furthermore, COVID-19 exhibits intrinsic coagulopathy associated with a risk of thrombotic events.

The detailed paper of Menizibeya *et al.* has summarized the following main pathways of CNS invasion of SARS-CoV-2: humoral and neural [37].

- The humoral pathway involves viral transport (RNAm, cytokines, toxic metabolites, peptides, and other molecules produced by SARS-CoV-2) by the circulatory system towards the CNS. These molecules may be generated within the lung, gastrointestinal system, and other tissues. Subsequently, the interaction of SARS-CoV-2 with the cerebral vascular endothelium leads to neuroinflammation and BBB dysfunction.
- The neural pathway is based on the neuro-modulation and neuro-signaling determined by the viral molecules which interact with neurons, various peripheral neuronal structures (such as the enteral ones), with microglia, cranial nerves (facial, vagus, glossopharyngeal and olfactory), which ultimately leads to CNS dysfunction. CNS viral neuroinvasion is also possible via peripheral nerve fibers.

The capacity of infecting various cerebral regions confirms the process of neuroinvasion. The olfactory epithelium shows high ACE-2 and protease expression, which allows binding, replication, and accumulation, suggesting that nasal swabs are adequate for viral detection during the initial stages of the infection. The olfactory pathway is the first one that may be involved in the neuroinvasion, neuroinfection and neuro-inflammation generated by SARS-CoV-2.

Accordingly, due to the existence of the previously mentioned possible pathways (humoral and neural) and the widespread presence of the ACE-2 receptor and endogenous proteases within cerebral tissue, the virus is able to generate neuroinflammatory cerebral lesions. The BBB becomes dysfunctional due to a subsequent lower ACE-2 expression, a higher activity of membrane protease produced by viral RNA, and antigenic peptides accumulation.

All of the aforementioned factors lead to cytokine and chemokine production and release, oxidative stress, and cerebral neurotransmission disorders, which may account for neurologic sequelae following COVID-19 infection. Acute respiratory failure may also lead to cerebral hypoxia and acute cerebral ischemia. Therefore, the mechanisms involved in COVID-19-associated CNS dysfunctions may be a direct consequence of the virus or the indirect result of a proinflammatory activity. Astrocyte involvement has also been considered by certain authors [38].

Astrocytic dysfunction, even in the absence of inflammation, may directly lead to neuronal dysfunction and loss of neuronal integrity, which is suggested by the high levels of neurofilaments in COVID-19 patients' blood [39, 40].

Conflict of Interest

The author confirms that there are no conflicts of interest.

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