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Review

Excitotoxicity and Neurological Post-COVID-19 Syndrome: Exploring Possible Connections of Pathophysiological Mechanisms

Rodrigo Portes Ureshino [1,2,*], Larissa Augusta de Sousa [1,2], Rafaela Brito Oliveira [1,2], Giulia Alves Saullo [1,2], Pedro Henrique Zonaro [1,2], Louise Newson [3], Carla Máximo Prado [4] and Roberta Sessa Stilhano [5]

1 Department of Biological Sciences, Universidade Federal de São Paulo, Diadema 09972-270, SP, Brazil; augustadesousalarissa@gmail.com (L.A.d.S.); rafaelaqmc@gmail.com (R.B.O.); giusaullo@gmail.com (G.A.S.); pedrozonaroo@gmail.com (P.H.Z.)
2 Laboratory of Molecular and Translational Endocrinology, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo 04039-002, SP, Brazil
3 Newson Global Ltd., Stratford-Upon-Avon CV37 6HB, UK; louise.newson@newsonhealth.co.uk
4 Department of Biosciences, Universidade Federal de São Paulo, Santos 11015-020, SP, Brazil; carla.prado@unifesp.br
5 Department of Physiological Sciences, Faculdade de Ciências Médicas da Santa Casa de São Paulo, São Paulo 01224-001, SP, Brazil; robertasessa@gmail.com
* Correspondence: rodrigo.portes@unifesp.br; Tel.: +55-11-55764848 (ext. 1045)

Abstract

Excitotoxicity is one of the factors that participates in neurodegeneration, impairing neuronal and glial cells' function, and leading to the development of chronic neurodegenerative diseases. The main mechanism of action lies in the overstimulation of excitatory receptors, especially the NMDA (N-methyl-D-aspartic acid) receptor, by glutamate, which promotes a massive influx of Ca^{2+} that is not sufficiently buffered by the intracellular machinery, or not released by mechanisms such as Ca^{2+} ATPase and plasma membrane Ca^{2+}/Na^{+} exchanger promoting, among other toxic effects, mitochondrial damage and an increase in reactive oxygen species (ROS). Notably, many cases reported of long COVID-19 describe significant brain alterations and neuropsychiatric disorders, including delirium, depression, etc., and patients required increased use of antidepressant or anxiolytic drugs, for example. In addition, emerging evidence links neurodegeneration as a potential long-term sequelae associated with an increased number of patients with cognitive disorders. This review analyzes data from the literature regarding brain alterations associated with post-COVID-19 syndrome and explores a potential link to the excitotoxicity pathways, due to its participation in neurodegeneration by homeostatic failure, and it is clearly present in various brain conditions, such as Alzheimer's and Parkinson's diseases.

Keywords: post-COVID-19; excitotoxicity; Ca^{2+}; neurodegenerative diseases; mitochondria

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1. Glutamate: From Neurophysiological "Master Key" Neurotransmitter to Excitotoxicity and Neurological Alterations

Glutamate is the most abundant excitatory amino acid in the Central Nervous System (CNS) and plays a dual role, both in neuronal transmission and, in excess, in triggering cell death. Firstly, as an excitatory neurotransmitter, glutamate released in the synaptic cleft activates its receptors and promotes the generation of an action potential on the membrane, promoting a rapid depolarization of the cell membrane. This results in a high and transient

intracellular cytosolic Ca^{2+} peak, with AMPA (β-amino-3-hydroxy-5-methylisoxazole) and kainate receptors as prominent constituents in this action due to their rapid kinetics and desensitization in millisecond intervals. Subsequently, the NMDA (N-methyl-D-aspartic acid) receptor (NMDAR) requires the co-agonist glycine [1] to be activated; then, at −70 mV resting membrane potential, there is the removal of the voltage-dependent Mg^{2+} blockade for the NMDA channel, which allows the influx of Ca^{2+} [2]. However, in the case of high glutamate concentration in the synapse, NMDAR overstimulation occurs, which can lead to increased cytosolic Ca^{2+} concentrations to toxic levels [3]. Following the glutamate release, the massive and prolonged influx of Ca^{2+} accumulates in the mitochondria, which in turn elevates reactive oxygen species (ROS) production and participates in the transition permeability by keeping the mitochondrial permeability transition pore (mPTP) open to release pro-apoptotic proteins stored in this organelle [4]. It has been found that in many neurodegenerative diseases, such as Parkinson's disease, cell death occurs and excitotoxicity is present [5,6]. Furthermore, in the context of neurological symptoms associated with COVID-19, elevated Ca^{2+}-activated enzymes such as proteases, kinases, and endonucleases have been proposed to be involved in neuronal deficits [7].

Mechanistically, in addition to its well-known action as a synaptic neurotransmitter, glutamate signaling is highly relevant in neuronal plasticity through the modulation of long-term potentiation (LTP), thus participating in the memory consolidation process [8]. It has been shown that Ca^{2+} ions may be related to hippocampal cell apoptosis in animal models of chronic sleep restriction (a reactive response to a psychiatric alteration, for example) during aging [9]. It is worth highlighting that astrocytes play a very important role in synaptic plasticity, through the control of neurotransmitter reuptake and recycling [10]. Glutamate activates metabotropic receptors: Group I (mGluR1 and mGluR5 receptors—GPCR, which increase PLC activity, resulting in increased intracellular Ca^{2+}), Group II (mGluR2 and mGluR3 receptors—GPCR, which reduce adenylyl cyclase activity, resulting in reduced cAMP), and Group III (mGluR4, mGluR6-8 receptors—GPCR, which reduce adenylyl cyclase activity, resulting in reduced cAMP); and ionotropic receptors. These neurons express receptors on their membranes, which are composed of NMDAR (NR1, NR2A-D) and AMPA (GluR1-4) receptors and Kainate (GluR5-7, KA1-2) receptors, whose expression is found differentially in brain structures. NR1 expression in the brain is widespread, but NR2 expression is denser in some brain structures [11]. Related to the aging process, in the striatum of elderly animals, Ca^{2+} homeostasis is altered in response to glutamate stimulation [12]. Other cells also take part in excitotoxic damage. For example, astrocytes use the excitatory amino acid transporter 2 (EAAT2) to reuptake the excess of glutamate released in the synaptic cleft [13,14], and its expression is regulated by NF-κB [15]. Regarding this protein, the neuroinflammation process (as discussed below) is mechanistically linked to NMDAR-mediated excitotoxicity, involving the *p53* and *c-myc* mRNA expression [16], and also the inhibition of NF-κB results in neuroprotective actions caused by glutamate excitotoxicity. The astrocyte function dysregulation can also lead to an increase in extracellular glutamate [17], and also with the reactivity of astrocytes in brain damage processes [18]. Interestingly, this process comes with the activation of microglia [19], which, in turn, can convert kynurenine into quinolinic acid (NMDAR agonist), which could contribute to exacerbating the excitotoxicity [20].

2. Consequences of Unbalance of Mitochondrial Ca^{2+} Homeostasis in Excitotoxicity

Mitochondria are the main cellular energy power source, also playing a role in the β-oxidation of fatty acids, in the regulation of cell death pathways and in Ca^{2+} homeostasis; in the context of this review and neurodegenerative processes, as mentioned above, when a

massive influx of Ca^{2+} via NMDAR over-stimulation occurs, it results in a disturbance of mitochondrial Ca^{2+} homeostasis. As such, due to the wide variety of cellular processes in which mitochondria are involved, mitochondrial dysfunction is a common feature of neurodegenerative diseases and is related to excitotoxicity [21]. Notably, 90% of intracellular ROS are produced in mitochondria as a consequence of the activity of the electron transport chain (ETC) and oxidative phosphorylation complexes. The main electron leakage occurs at the level of respiratory complexes I and III (for review [22]). As a result, increased radical production during aging can trigger apoptosis. Consequently, aged brains show increased mPTP opening and increased release of pro-apoptotic factors into the cytosol (for review [23]). As mentioned earlier, the massive influx of Ca^{2+} into cells via the NMDAR can lead to apoptosis by increasing ROS generation. For example, in Parkinson's disease, oxidative stress also plays an important role in the degeneration of dopaminergic neurons, including mitochondrial dysfunction and excitotoxicity [24]. Another 2005 study showed that mutant Huntingtin (mHtt) expression in astrocytes was toxic to healthy neurons, which may occur due to the inability of these astrocytes to protect neurons from glutamate toxicity, leading to excitotoxicity [25]. Notably, in the basal ganglia affected in both neurodegenerative diseases, the striatum has a high density of glutamate receptors with afferent fibers from the neocortex, hippocampus, amygdala, and thalamus [26].

An interesting finding is that, during the aging process, the state 3 (ADP-dependent) of respiration in the hippocampus is substantially decreased, likewise the activity measured in complexes I and IV of the ETC [27]. This finding is interesting because, during oxidative phosphorylation, electron escape can occur in complexes I and III of the respiratory chain, resulting in the reduction in molecular oxygen to the superoxide radical (O_2^-) in the mitochondrial matrix. Furthermore, ROS can lead to dysfunction in Ca^{2+} transport mechanisms [28], forming an alternation or sequence of effects that can cause serious cellular damage. Furthermore, to combat oxidative stress, cells intrinsically have some antioxidant systems, such as glutathione peroxidase, and the failure of these systems can lead to cell damage, sometimes as excitotoxicity [29].

Mitochondrial Ca^{2+} plays an important role in the activation of citric acid cycle dehydrogenases and in ATP production [30], but, on the other hand, it can increase the production of ROS. Mitochondrial location is a contributing factor in determining its oxidative imbalance and, consequently, peroxidation by oxygen radicals [31]. Therefore, impaired mitochondrial Ca^{2+} homeostasis, in part due to massive Ca^{2+} influx via NMDAR, can make cells more vulnerable to cell death.

3. Neurological Sequelae of SARS-CoV-2 Infection

3.1. CNS Infection

For SARS-CoV-2 infection of host cells, first, the Spike protein's receptor-binding domain (RBD) binds to the angiotensin-converting enzyme 2 (ACE2) receptors [32]. This enzyme is found in cellular receptors in lung tissue, nasal mucosa, and oral mucosa. Furthermore, it is found in astrocytes, oligodendrocytes, and neurons, and is widely expressed throughout the brain, including the substantia nigra, ventricles, the middle temporal gyrus located in the temporal lobe, the olfactory bulb, and the posterior cingulate cortex [33]. Regarding the invasiveness of the CNS, it has been shown that cells that form the blood–brain barrier (BBB) also express ACE2, such as endothelial cells and pericytes (for review [34]). One proposed mechanism for CNS invasion by SARS-CoV-2 is transcellular migration, which involves the virus binding to its receptors, ACE2, basigin (BSG), or neuropilin-1 (NRP-1), on endothelial cells of the cerebral microvasculature, subsequently crossing them by transcytosis [35].

Furthermore, SARS-CoV-2 infection can promote the hyperactivation of glial cells, which may result in the disruption of the tight junctions of the BBB [36] and then increased permeability, which contributes to the virus's access to the CNS [37]. In addition to this mechanism, infected immune cells transport the virus across the endothelial cells of the BBB to the CNS via an ICAM-1-dependent mechanism, whose expression is increased by TNF-α. This interaction promotes the activation of matrix metalloproteinases, especially MMP-9, contributing both to the leakage of these cells and to the degradation of membrane components [38]. Subsequently, leakage across the barrier can lead to the entry of pro-inflammatory cytokines, promoting a neuroinflammatory state [34].

SARS-CoV-2 can use the olfactory epithelium to gain access to the CNS [39]. SARS-CoV-2 appears to exploit this neuromucosal interface as an entry point into the CNS [39]. For comparison, using MHV-CoV (murine hepatitis virus) via intranasal inoculation, Singh et al. found the virus in CNS structures such as the limbic system and the brainstem, which could use the olfactory nerve for CNS access [40], as noticed with SARS-CoV-2 in the rhesus monkey [41,42].

Finally, retrograde transport along cranial nerves such as the optic, trigeminal, and vagus nerves is another route of SARS-CoV-2 brain infection [43]. Although human data are limited, rodent studies have shown ACE2 expression in the vagus nerve complex, suggesting a possible route of SARS-CoV-2 dissemination to the brainstem [44]. Alternatively, Chen et al. demonstrated that, once on the ocular surface, SARS-CoV-2 can access the brain via the nasolacrimal duct [43].

3.2. Neurological Sequelae and Post-COVID-19

The findings related to the SARS-CoV-2 infection and its long-term consequences are still unclear; however, evidence below offers a perspective on possible neurological sequelae. During the COVID-19 period, patients without a prior neuropsychiatric history presented with attention difficulties, insomnia, fatigue, hysteria, and delusions, occasionally leading to severe behavioral changes such as suicide attempts [45–49]. Patients admitted to intensive care units (ICUs) presented with agitation (69%) and signs of corticospinal tract injury (67%), suggesting a definite association between COVID-19 and encephalopathy [50]. A cohort study involving over 100,000 infected patients estimated that, one year following acute SARS-CoV-2 infection, individuals exhibited an increased risk of a range of neurological sequelae, spanning from encephalitis or encephalopathy to syndromes such as Guillain-Barré and cognitive disorders, among others. The hazard ratio for any neurological sequela was estimated at 1.42 compared to the study's control groups. These elevated risks were observed even in individuals who did not require hospitalization during the acute phase, reinforcing the systemic and persistent impact of SARS-CoV-2 on the nervous system [51]. Another study found that 13.5% of COVID-19 patients developed neurological disorders [52], and also dementia, hallucinations, seizures, and encephalopathy [51,53–55]. Therefore, the neurological sequelae of COVID-19 have been defined by multiple terms and are part of post-COVID-19 syndrome, or long COVID [56–58], as it affects many individuals after several years [59], which can also be a consequence of inflammation caused by SARS-CoV-2 infection [60].

Furthermore, many COVID-19 survivors have reported persistent symptoms and/or the development of long-term symptoms after infection. The manifestations and impact of neurological diseases related to SARS-CoV-2 require clinical, diagnostic, and epidemiological studies [61]. Emerging evidence suggests that patients with COVID-19 also present neurological symptoms and complications [50,62,63], such as memory loss [64,65]. Several structural neurological abnormalities can persist for a long time after acute COVID-19 infection, which is part of the long spectrum of COVID-19 [57,66,67].

Among the studies analyzed in this review, Bianchetti et al. presented a comprehensive summary of the clinical manifestations of COVID-19 in patients with dementia. Among 82 patients diagnosed with dementia, the most common initial symptoms of COVID-19 were delirium (67%) and worsening of functional status (56.1%). On the other hand, typical COVID-19 symptoms, such as fever (47.6%), dyspnea (43.6%), and cough (13.4%), were less common in patients with dementia [68], which may suggest a neurological vulnerability to viral infections. Furthermore, comprehensive neuropsychological assessments identified neurocognitive disorders (NCDs) in approximately 59.6% of participants, with 50% presenting severe NCDs. In the cognitive domain, learning difficulties, memory, and executive function impairments are frequently observed, affecting 60.7% of individuals with NCDs. Other reported cognitive impairments include complex attention deficit (51.6%), language disorders (35.5%), and perceptual-motor impairment (29.0%) [69]. Overall, 53% of patients presented at least one domain of cognitive impairment two months after resolution of COVID-19. Individuals with COVID-19 presented higher volumes of hyperintensity in white matter, which were associated with worse baseline memory function and total cardiovascular risk factors. In fact, COVID-19 results in hyperinflammation and associated coagulopathy, since one of the primary mechanisms of brain injury is microvascular disorder. Evidence indicates that the endothelial basal lamina gets thinner; there is fibrinogen leakage, and microhemorrhages within the brainstem and olfactory bulbs [70]. Lower delta waves on the electroencephalogram at baseline have been suggested as predictors of worse cognitive function at follow-up [71]. Since the integrity of subcortical white matter is essential for maintaining normal cognitive function [72]. In summary, the neurological landscape of COVID-19 is characterized by a complex interplay between multiple neuroinvasion pathways, including hematogenous dissemination associated with the blood–brain barrier permeability and retrograde axonal transport.

3.3. Brain Cell Alterations Due to COVID

Since many cell types are infected by SARS-CoV-2, including neurons [73], studies on the physiology of the CNS and how neuronal cells infected by SARS-CoV-2 are affected are of great scientific relevance, as is understanding the viral impact on these cells. In this sense, a post-mortem study of COVID-19 patients found the presence of hypertrophic astrocytes and activated microglia. The same study reported the presence of activated microglia adjacent to neurons, suggesting neuronophagia in the olfactory bulb, the dorsal motor nucleus of the vagus nerve, the substantia nigra, and the pre-Bötzinger complex of the spinal cord [70]. In addition to aberrantly activated microglia, COVID-19 significantly reduced the complexity, length, and total number of astrocytic processes and significantly increased the size of astrocyte cell bodies in infected patients [74]. Notably, mild respiratory infections with SARS-CoV-2 activated microglia in the subcortical white matter of a mouse model, leading to the loss of oligodendrocyte precursors and mature oligodendrocytes, followed by the loss of myelinated axons, thus impairing the structure and function of the neuronal network [75]. These findings underscore that the pathophysiology of CNS involvement in COVID-19 is a multifaceted interplay between vascular integrity, glial reactivity, and neuronal viability.

Astrocytes may play a key role in the neuropathology of COVID-19, being involved in virus dissemination in the CNS, immune responses, and neuronal function [76]. Another study analyzed the long-term sequelae of COVID-19 in a murine model induced by murine hepatitis coronavirus type 1 (MHV-1). It observed alterations in astrocytes, with increased size, reactive microglia, hyperphosphorylation of TDP-43 and tau, and decreased synaptic protein synaptophysin-1, suggesting a possible long-term impact of SARS-CoV-2 infection on compromised neuronal integrity [77]. Astrocytes are essential for neurotransmitter

recycling, a critical function in preserving synaptic transmission and neuronal excitability. They play a crucial role in regulating glutamate levels in the brain [13,14]. Changes related to these cells can impair the recycling of these neurotransmitters, which could compromise metabolic processes important for the proper functioning of the central nervous system in the long term.

The cellular changes resulting from neurological infection caused by SARS-CoV-2 can encompass not only astrocytic hypertrophy, excessive microglial activation, and neurophagic events in neuronal tissues, but also disturbances in mitochondrial function within CNS cells. The SARS-CoV-2 spike protein can induce mitochondrial damage in the brain's endothelial cells, impairing their respiratory activity and contributing to the heterogeneous neurological manifestations observed in individuals with COVID-19. In addition, fragments of the viral spike protein exhibit toxic amyloidogenic properties and can co-aggregate with Aβ, potentially exacerbating the pathology of Alzheimer's disease. This interaction can promote subsequent events such as Aβ amyloidosis, tauopathy, neuroinflammation, and dysregulated immune responses, ultimately contributing to long COVID-19 [78]. Therefore, the structural degradation of the microvascular basement membrane, coupled with the morphological and functional remodeling of astrocytes and microglia, establishes a dysfunctional microvasculature-glia environment. This gliovascular disruption not only accounts for the acute encephalopathy and clinical sequelae observed in hospitalized patients but also provides a mechanistic foundation for the persistent cognitive deficits and neurodegenerative-like features of long COVID-19.

4. Dysregulation of Ca^{2+} Mobilization and Neuronal Death: A Possible Association with Post-COVID-19 Syndrome

Cellular signaling and homeostasis are driven by the activation/deactivation of various enzymes, with ion mobilization playing a crucial role in these processes. Ca^{2+} is a "key" mediator in neural transmission, maintaining the resting potential (−80 mV in neurons) and establishing electrophysiological balance with K^+ and Na^+. It is not surprising that this ion may play a role in viral infection, since the cleavage of the S protein exposes a fusion peptide, and experiments suggest that Ca^{2+} plays a role in this fusogenic activity through a Ca^{2+} binding site with conserved glutamic acid and aspartic acid residues [79]. Therefore, alterations in Ca^{2+} levels in host cells can alter cellular physiology, as well as facilitate viral entry and promote coronavirus infection (for review [80]). As an example, Simpson et al. suggest that some virus structures contain a flexible surface loop that binds to Ca^{2+}, which may aid virus entry and infection [81].

Interestingly, some viruses increase the mobilization of Ca^{2+} from the ER, such as Poliovirus [82] and HSV [83]. Other viruses, such as the Japanese encephalitis virus (JEV), can activate NMDAR and promote encephalitis [84]. The lack of research on SARS-CoV-2-related excitotoxicity in these cases needs to be addressed, as some other viruses exhibit this pattern related to cell death and Ca^{2+} overload. It is worth noting that a possible strategy to be investigated could favor the use of Ca^{2+} channel blockers [80,85], but this issue remains controversial. A study with a large number of patients found that Ca^{2+} channel blockers, alone or in combination with other medications (statins, angiotensin-converting enzyme inhibitors), reduced mortality from COVID-19 [86]. On the other hand, another meta-analysis indicated that these compounds were not associated with the outcome of COVID-19 mortality, while subgroup analysis showed that Ca^{2+} channel blockers are associated with a decrease in mortality in hypertensive patients with COVID-19 [87].

The elderly are the most affected by this disease and have the highest mortality rate from COVID-19. In this sense, since aging is the main known factor for the development of neurodegenerative diseases, there may be a risk of comorbidity, given that many studies

have shown that COVID-19 infection is associated with the worsening, or even acceleration, of symptoms during the progression of the most common neurodegenerative diseases (e.g., Parkinson's disease and Alzheimer's disease) [88–92]. On the other hand, comorbidity in patients with Alzheimer's disease and Parkinson's disease has been reported by [93–96], who presumably are the most fragile and require medical support (sometimes in hospitals), being infected by SARS-CoV-2.

Literature data correlate alterations in Ca^{2+} signaling and apoptosis in Alzheimer's disease [97,98] and in other neurodegenerative diseases [99], mainly associated with the aging process. In line with this ionic mobilization, as discussed earlier, astrogliosis and activated microglia, which are related to neurodegeneration and brain aging, play a role in excitotoxicity [100]. Furthermore, along with hypertrophic astrocytes, activated microglia were found in COVID-19 patients, related to microvascular injury [70], which may be involved in neuropathology [76,101]. In addition, a characterization of astrocytes was made by [74], configuring an altered phenotype. Therefore, it is well known that reactive astrocytes are associated with a worse prognosis, considering neurodegenerative processes [17]. Regarding alterations in the CNS and neuronal connectivity (e.g., synaptogenesis), Ca^{2+} is crucial for LTP, as mentioned earlier, and it is important to investigate the consequences of this absent binding. It is important to highlight that Fernández-Castañeda et al. observed notable alterations in the CNS (such as elevated cytokines, impaired hippocampal neurogenesis, etc.) in a mouse model infected with SARS-CoV-2 [102]. In addition, other harmful factors, such as elevated ROS, excitotoxicity, and inflammation, contribute to the development of neurological disorders, and long COVID-19 may be associated with neurodegeneration (for review [103]). Figure 1 summarizes the proposed mechanism for the possible association between neuroCOVID and excitotoxicity.

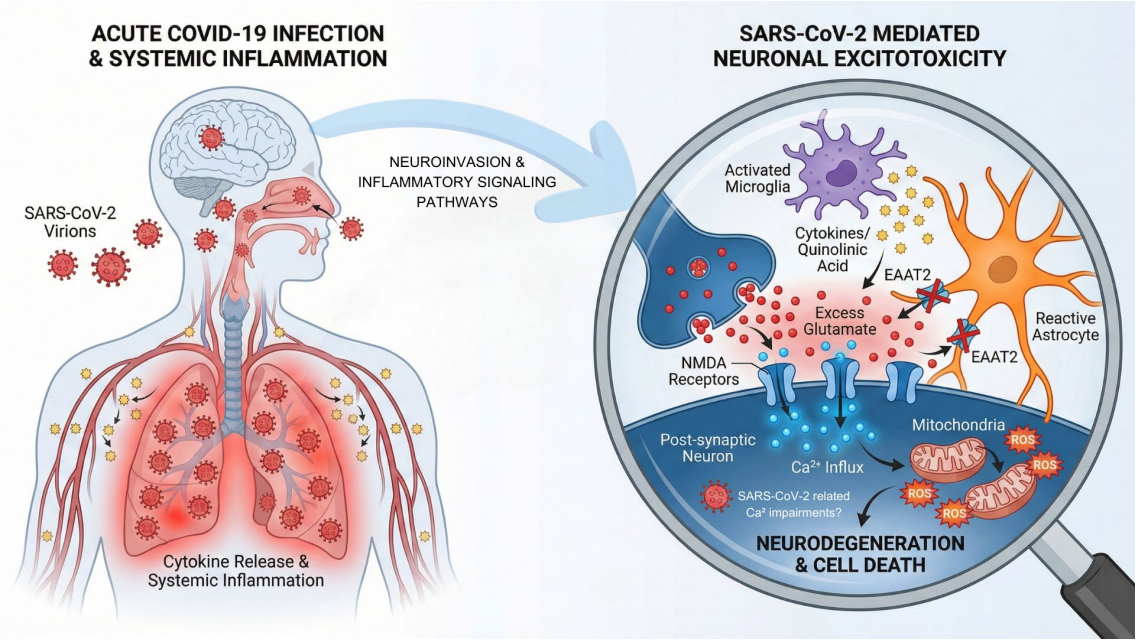


Figure 1. Integrative model of SARS-CoV-2-induced neuronal excitotoxicity and the pathophysi-ology of post-COVID-19 syndrome. This diagram illustrates the pathophysiological cascade extending from systemic infection to molecular neurodegeneration. Left Panel—Macroscale context: Exposure to SARS-CoV-2 triggers an acute respiratory infection and a subsequent systemic inflammatory response. Transition: These systemic signals, along with neuroinvasion pathways, activate neuroinflammatory signaling pathways within the Central Nervous System (CNS). Right Panel—Microscale mechanism: The magnified tripartite synapse highlights the disruption of glutamate homeostasis. Activated microglia release pro-inflammatory cytokines and neurotoxic metabolites, such as quinolinic acid (an

NMDAR agonist), while reactive astrocytes exhibit impaired glutamate clearance due to the down-regulation or dysfunction of glutamate transporters (EAAT2/GLT-1). This results in excess synaptic glutamate, leading to the overactivation of NMDA receptors (NMDAR). The consequent massive influx of Ca^{2+}—indicated as "SARS-CoV-2-related Ca^{2+} impairments"—triggers intracellular cascades, including mitochondrial dysfunction and increased production of reactive oxygen species (ROS). Collectively, these mechanisms culminate in synaptic loss, neuronal death, and the clinical manifestations of neurological post-COVID-19 syndrome, such as cognitive impairment and delirium.

5. Conclusions

Much evidence suggests a possible association between neuroCOVID and intrinsic cascades of events that occur under neuroinflammation and disruption of ionic homeostasis, particularly through the excitotoxicity in neurodegenerative conditions. In this sense, Ca^{2+} signaling is essential for a myriad of processes involving cell survival and neuroplasticity (such as LTP), and can even activate proteases, kinases, phosphatases, endonucleases, etc., some of them related to degradative processes (such as calpains). In addition, massive cytoplasmic Ca^{2+} entry leads to mitochondrial overloading, impairing ATP function or raising ROS levels, which, in some cases, can be unbalanced by SARS-CoV-2-mediated microvascular alterations and inflammation, also involving microglia and astrocytes, with the participation of NMDAR. These cellular alterations suggest that impaired neurotransmitter homeostasis and mitochondrial failure are important drivers of neurological impairment following SARS-CoV-2 infection.

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