Could SARS-CoV-2 Spike Protein Be Responsible for Long-COVID Syndrome?

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Abstract

SARS-CoV-2 infects cells via its spike protein binding to its surface receptor on target cells and results in acute symptoms involving especially the lungs known as COVID-19. However, increasing evidence indicates that many patients develop a chronic condition characterized by fatigue and neuropsychiatric symptoms, termed long-COVID. Most of the vaccines produced so far for COVID-19 direct mammalian cells via either mRNA or an adenovirus vector to express the spike protein, or administer recombinant spike protein, which is recognized by the immune system leading to the production of neutralizing antibodies. Recent publications provide new findings that may help decipher the pathogenesis of long-COVID. One paper reported perivascular inflammation in brains of deceased patients with COVID-19, while others showed that the spike protein could damage the endothelium in an animal model, that it could disrupt an in vitro model of the blood-brain barrier (BBB), and that it can cross the BBB resulting in perivascular inflammation. Moreover, the spike protein appears to share antigenic epitopes with human molecular chaperons resulting in autoimmunity and can activate toll-like receptors (TLRs), leading to release of inflammatory cytokines. Moreover, some antibodies produced against the spike protein may not be neutralizing, but may change its conformation rendering it more likely to bind to its receptor. As a result, one wonders whether the spike protein entering the brain or being expressed by brain cells could activate microglia, alone or together with inflammatory cytokines, since protective antibodies could not cross the BBB, leading to neuro-inflammation and contributing to long-COVID. Hence, there is urgent need to better understand the neurotoxic effects of the spike protein and to consider possible interventions to mitigate spike protein-related detrimental effects to the brain, possibly via use of small natural molecules, especially the flavonoids luteolin and quercetin.

Keywords

ACE2 · Antibodies · Blood-brain barrier · Brain · Coronavirus · Endothelial cells · Receptor · Spike protein

Introduction

The SARS-CoV-2 infects cells by first binding to its surface receptor, angiotensin converting enzyme 2 (ACE2), via its corona spike protein [1]. The S protein is trimeric and catalyzed fusion between the viral and host cell membrane; this “prefusion” trimer has three receptor-binding domains (RBD), while the post fusion structure expresses N-linked glycans that may serve to protect against immune responses [2]. Infection then leads to a complex immune response that involves the release of a “storm” [3, 4] of pro-inflammatory cytokines [3–11], especially IL-6 [12–15] and IL-1β [16, 17] leading to the development of COVID-19 [3, 18]. Most infected patients develop antibodies against the spike protein, but immune protection against SARS-CoV-2 may involve more than neutralizing antibodies [19].

A prospective study of more than 3,000 healthy members of the US Marines Corps concluded that those sero-positive could still be infected but had only 20% the risk of subsequent re-infection as compared to those who were seronegative [20]. It is not known if individuals who get re-infected do not mount sufficient neutralizing antibodies or lack some other aspect of antiviral immunity. New data from immunized individuals indicate that the rate of re-infection varies depending on the type of vaccine used [21]. There is
emerging evidence of reduced neutralization of some SARS-CoV-2 variants [22].

**Hypothesis/Theory**

Some of the damaging effects of SARS-CoV-2, especially in the brain, may be due to direct action of the Spike protein, acting alone or in conjunction with other mediators such as inflammatory cytokines, on target cells.

**Long-COVID Syndrome**

It is now recognized that many patients infected with SARS-CoV-2 develop a post-acute syndrome a few months after the initial infection known as “post-acute COVID” [23] or “long-COVID” [23–26]. Long-COVID occurs in 30–50% of COVID patients [23, 27–30] and is characterized by multisystem symptoms, primarily persistent fatigue and cognitive impairment [31] that varied considerably among patients [32] and were more common with increasing age and female sex [29]. These persistent symptoms should not be confused or misinterpreted as persistent infection that has been reported in immunocompromised hosts [33]. Nevertheless, patients with long-COVID have not recovered even by 7 months post infection and continue to suffer mostly from systemic and neurological symptoms [34].

Long-COVID is particularly associated with neurological [35–43], neurodegenerative [38, 44, 45], psychiatric [46–52], and cognitive [47–57] problems, especially brain fog [23, 25, 26, 46, 58–62]. In fact, over 90% of patients who were initially hospitalized for COVID-19 and had neurological symptoms had significantly worse outcome 6 months later [63]. Even though some of the mental fatigue experienced by long-haulers may be due to the perceived stress [64], the extent of this disability is unlike any other medical condition known.

In spite of early impressions that long-COVID may develop only in those patients who were hospitalized and intubated, increasing evidence indicates that long-COVID can develop regardless of the severity of the original symptoms [61, 65] and has been considered the “next health disaster” in the USA [66]. So far the duration of long-COVID symptoms is not known, but recent data indicate that it may depend on antigen persistence [67] and a sustained specific immune responses to SARS-CoV-2 [68].

The neurologic effects of COVID-19 may be due to SARS-CoV-2 entering the brain, but the pathways of such neurotropism are still unclear [69, 70]. One possibility is that the virus crosses or damages the blood-brain barrier (BBB) [71], accompanied by basement membrane disruption, in K18-hACE2 transgenic mice infected with SARS-CoV-2 [72]. Similar findings were reported independently, and it was also shown that the virus was detected in human cortical neurons [73]. In another study, a fragment specific to SARS-CoV-2 was amplified from cultures of a brain specimen from a deceased patient with COVID-19, and associated pathology showed neuronal necrosis and glial hyperplasia [74]. Alternatively, the virus could enter from the nose by crossing the neural-mucosal interface of the olfactory nerve [75] and enter the brain via the olfactory nerve tract [76]. Viral entry into the brain via gustatory-olfactory trigeminal pathway eventually compromising the BBB was recently reported in deer mice infected with SARS-CoV-2 [77].

The effect of SARS-CoV-2 to the brain is also not well understood. One paper showed the presence of megakaryocytes in cortical capillaries that could lead to brain ischemia [79] and subsequent cerebrovascular events [80–82]. In the autopsy report of an infant who died with COVID-19, there was evidence of cortical atrophy and severe neuronal loss, and findings were restricted to capillaries of the choroid plexus [83]. A recent paper did not document any molecular traces of SARS-CoV-2 in the brains of deceased patients with COVID-19, but detected choroid plexus perturbations associated with pathologic morphological changes in the microglia [84]. In addition to the evidence discussed above of neuronal damage due to SARS-CoV-2, a paper reported that the virus can enter a 3D human brain organoid and preferentially targets neurons resulting in their death [85]. Such pathology may be explained by the expression of the ACE2 receptor by human glial cells and neurons [86], exacerbated through the activation of the complement and kinin systems [87].

Increasing evidence indicates the involvement of neuroinflammation [71, 88, 89] that may damage brain blood vessels [90, 91], as well as brain cells [88, 92, 93], possibly via activation of microglia [94, 95] and mast cells [96]. In fact, long-COVID could be considered a state of “brain autoimmunity” [22].

In summary, the effect of SARS-CoV-2 to the brain could be direct via invasion or indirect effect via damaging endothelial cells and pericytes or via activation of neuroimmune responses as has been invoked for neurologic complications following HIV [97].
Direct Effects of Spike Protein

An alternative explanation of the CNS effect of SARS-CoV-2 may be due to direct effects of the spike protein. The spike protein is made up of the S1 subunit containing a receptor-binding domain (RBD) that attaches to ACE2 and the S2 subunit containing a transmembrane anchor that mediates fusion of viral and host cell membranes [1]. Most infected patients develop antibodies that neutralize the spike protein to various extents. A recent paper reported that blood of patients infected with SARS-CoV-2 contained, in addition to antibodies against the RBD that were protective, also antibodies against the N-terminal domain (NTD) of the spike protein that induced the open conformation of the RBD enhancing its binding ability and infectivity in vitro using cultured cells [98]. A more recent study of molecular modeling using an antibody from a symptomatic COVID-19 patient concluded that there was higher NTD binding with the delta variant resulting in antibody-dependent enhancement (ADE) [99]. Such interactions, where antibodies can neutralize one serotype but are less potent at neutralizing another, are known to increase the chances of ADE to the new serotype [100]. Even though ADE remains controversial, a recent paper reported that virus-mimicking anti-idiotype antibodies present after infection or after vaccination may potentially explain long-COVID symptoms [101]. These findings may potentially explain why those vaccinated against the original Wuhan SARS-CoV-2 strain and then exposed to the Delta variant may still get infected. An alternative or additional explanation may be the fact that immunity to vaccines has been reported to decrease over time [102, 103].

It is not yet known if the spike protein is released extracellularly after the SARS-CoV-2 infects its target cells. Given the absence of infection of the brain discussed above, the neuropathologic findings may be due to the SARS-CoV-2 spike protein. Indirect evidence of its presence within the CNS may be the detection of anti-SARS-CoV-2 antibodies in the CSF of two children who died with COVID-10 and had subacute neuropsychiatric symptoms [104], even though such antibodies may have crossed a disrupted BBB. Free spike protein could have a number of direct pathologic actions on different cell types (Fig. 1A). These include direct stimulation of peripheral nerves [105] and stimulation of release of pro-inflammatory and vasoactive mediators [106, 107], especially platelet-activating factor (PAF) [108, 109].

A number of papers have reported direct pathologic effect of the spike protein by itself (without being part of the coronavirus). One paper reported that the spike protein could damage the endothelium in an animal model [110], while another paper showed that recombinant S1 RBD can damage mouse brain endothelial cells in vitro by inducing degradation of endothelial junction proteins, thus affecting endothelial barrier function [111]. A recent paper reported rapid internalization of S1 RBD and of the spike RBD active trimer by cultured human brain microvascular endothelial cells, followed by increased permeability of transferrin and dextran, as well as mitochondrial damage [112]. Another recent paper using a 3D-BBB microfluidic model showed that S1 upregulated ACE2 expression and triggered RhoA activation, a key molecule regulating endothelial cytoskeleton [113]. Yet, another paper reported that spike-transfected human epithelial cells showed increased senescence-associated secretory and inflammatory proteins [114].

Two other papers reported that the spike protein could disrupt the barrier function in an in vitro model of the blood-brain barrier (BBB) [115] and that the S1 protein can actually cross the BBB and enter the brain in mice [116] (Fig. 1A). Using transgenic mice expressing the human sigma protein, it was shown that intranasal infection with SARS-CoV-2 rapidly induced ischemic-like reactivity in brain pericytes and the S protein reached the brain of the mice [117].

In addition to direct damage, the spike protein appears to share antigenic epitopes with human molecular chaperons resulting in autoimmunity against endothelial cells [118]. Moreover, a recent paper showed that spike epitopes could form heterodimeric complexes with selected human glial proteins [119]. Interestingly, it was shown that three recombinant sigma protein peptides exhibited molecular interactions with acetylcholinesterase and antioxidant enzymes both in silico and in tad poles in vivo [120].

Interestingly, symptoms experienced by long-COVID patients, especially cognitive dysfunction [121–123], are similar [106] to those present in patients with mast cell activation syndrome (MCAS) [124, 125], in whom mast cells can be stimulated by environmental and stress triggers [126], including viruses [127] such as SARS-CoV-2 [107, 128]. Mast cells are located perivascularly in close proximity to neurons, especially in the hypothalamus [129, 130], where functional mast cell-neuron interactions have been documented [130, 131]. Mast cells also interact with microglia [132] leading to their activation [133] and neuroinflammation [134].

SARS-CoV-2 binding may not be limited to the ACE2 receptor. New evidence indicates that the spike protein also binds to heparan sulfate (HS) molecules expressed on the surface of target cells, with mutant variants having higher binding affinity to HS [135]. This binding may be due to the fact that the SARS-CoV-2 spike protein contains four more positively charged and five fewer negatively charged residues than SARS-CoV, thus increasing the binding affinity of SARS-CoV-2 for HS [136]. Apparently, binding to
HS allows the virus to reach the ACE2 receptor, and the RBD portion of the spike protein can engage both HS and ACE2 without dissociation of one or the other ligand [137]. The S1 subunit can also bind to the surface glycoprotein neuropilin-1 (NRP-1), thus increasing infectivity, but also dysregulating angiogenesis, immune responses, and neuronal development [138, 139]. Different coronavirus variants have evolved more efficient electrostatic interactions to allow them to bind to the ACE2 receptor [140]. SARS-CoV-2 also appears to become “pre-activated” by the proprotein convertase furin, thus bypassing the target cell proteases for entry [141].

SARS-CoV-2 can do additional damage by activating toll-like receptors (TLRs), especially TLR2, leading to secretion of pro-inflammatory cytokines independent of viral entry [142, 143]. Such immune-mediating molecules could contribute to neurologic symptoms [144] as a result of or in addition to the action of the spike protein. Moreover, activating TLR4 increases expression of ACE2 [145] further enhancing viral infectivity in an autocrine loop. Activation of TLRs may not only involve activation of inflammasomes [146], but also activation of the mammalian target of rapamycin (mTOR) complex [147, 148], which is invoked in the pathogenesis of many neuropsychiatric diseases [149] (Fig. 2). Increased levels of a number of pro-inflammatory cytokines have been detected in the CSF of COVID-19 patients [150], especially IL-6 [150, 151]. In fact, use of an anti-IL-6 antibody or IL-6 receptor antibody reduced neuronal injury in a mouse model, accompanied by inflammation and neuronal death unrelated to hypoxia [152]. Integration of serum levels of IL-6
and heparin-binding protein were shown to have significant predictive value for severity of COVID-19 [153].

A recent paper reported cloning and expressing 26 of the 29 proteins encoded by the SARS-CoV-2 genome and showed most proteins, especially non-structural protein (NSP) 2, 5, and 7, induced significant changes in endothelial permeability [154]. These findings imply that SARS-CoV2-associated proteins other than the spike protein may contribute to pathologic effects on their own, sequentially or synergistically with the structural sigma protein.

Lastly, a recent paper analyzed human fetal expression of six different S protein “interactors” and showed weak expression of ACE2 and TMPRSS2, but high expression of furin with peak expression 12–26 weeks post conception; moreover, using publically available single-cell RNA sequencing datasets, it was shown that these interactors showed higher co-expression with neurons [155]. This finding indicates that the spike protein can adversely affect the developing brain and potentially lead to neurologic complications in neonates of infected mothers [156], including autism spectrum disorder [157].

Discussion

A major unaddressed issue, especially with respect to the pathogenesis of long-COVID, is whether the spike protein that enters the brain or is expressed in neurons and glial cells can activate microglia directly or via stimulation of mast cells leading to neuro-inflammation [158]. This pathogenetic process would go on unhindered in the absence of any neutralizing antibodies since they do not cross the BBB, thus contributing to the pathogenesis of long-COVID. Moreover, such spike protein-induced neurocognitive damage could be worse in vulnerable populations like those with minimal cognitive impairment [159] or others suffering from traumatic brain injury [160].

There are presently no biologics that can block SARS-CoV-2 binding to its receptor(s). Certain biologics aimed at blocking IL-6 [161] or IL-1 [162] have been reported to improve clinical status of patients with COVID-19 However, a meta-analysis of clinical trials using IL-6 antagonists as an add-on to usual care did not reduce the risk of stroke [163], and a recent double-blind, randomized placebo-controlled study showed no benefit of an IL-6 blocker [164]. This conclusion may not be surprising as these humanized antibodies are not likely to cross the BBB unless it has already been disrupted. It is interesting that a main source of IL-6 is the mast cells [165–167], which have been reported to secrete it after stimulation with IL-1 [168] and acute stress [169]. Moreover, IL-6 can be constitutively released from human mast cells bearing the D816V-KIT mutation [170] and act on mast cell in an autocrine fashion to stimulate their proliferation [171].

This manuscript does not attempt to review and discuss all possible drugs, biologics, or natural molecules that could interfere with SARS-CoV-2 binding and its effects on target cells. Rather, it focuses on certain natural molecules for...
which there is sufficient basic and clinical evidence supporting their possible usefulness, both in prevention and treatment, especially in long-COVID. A number of recent reviews have discussed the potential use of natural molecules in that capacity [172–174]. Some simulation and in vitro studies have reported the potential benefit of small molecules found in Ginkgo biloba, such as the flavonoid quercetin discussed later. For instance, extracts from Ginkgo biloba leaves were identified as potential inhibitors of SARS-CoV-23CL(pro) using large-scale screening [175]. Another Ginkgo biloba extract was reported to block TNFα-induced reactive oxygen species from human aortic endothelial cells [176]. The Ginkgo biloba extract EGb 761 was beneficial in generalized anxiety disorder [177] and dementia [178], actions that may be useful for the neuropsychiatric aspects of long-COVID. Ginkgolic acid (GA) was shown to inhibit the fusion and synthesis of viral proteins [179]. Other studies have shown that green tea catechins could be useful in COVID-19 [180, 181], especially against entry of SARS-CoV-2 [182]. The broccoli extract sulforaphane inhibited expression of IL-6 and IL-8 induced by the SARS-CoV-2 spike protein in bronchial epithelial cells [183].

Certain natural flavonoids [184] have been proposed as prophylaxis or treatment against COVID-19 [185–189]. Such flavonoids are found in green plants and seeds and possess potent anti-oxidant, anti-inflammatory, and cytoprotective properties [184]. However, their consumption as part of the diet does not provide sufficient systemic levels. However, there are a number of sources of pharmaceutical-grade purity (>98%) using different biomasses such as Citrus limon, Cynara cardunculus (artichoke), oregano, and Saphora japonicum.

In particular, a number of studies using in silico approaches identified the flavonoid quercetin and the structurally related flavone luteolin as a potential strong blockers of RBD [190–192]. Luteolin and some of its methylated analogues have a number of beneficial actions with respect to long-COVID: broad antiviral properties [193–195], inhibition of coronavirus entry [127, 196, 197], and inhibition of the serine protease required for spike protein processing [198, 199]. Furthermore, luteolin inhibits activation of both microglia [200–203] and mast cells [204, 205] via inhibition of signaling pathways involving the inflammasome [206, 207] and mTOR (Fig. 2) in both mast cells [205] and microglia [203]. The novel luteolin structural analogue tetramethoxyluteolin (methoxy-luteolin) is an even more potent inhibitor than luteolin [203–206].

With respect to long-COVID especially, luteolin could prevent neuro-inflammation [208–211], is neuroprotective [208, 210, 212, 213], and reduces cognitive dysfunction [214–218], especially brain fog [58, 60, 62]. Quercetin has been discussed in a few recent studies [219, 220], including an open-label clinical study showing good tolerability and benefit [221]. A double-blind, placebo-controlled, randomized study using a liposomal preparation of luteolin (PureLut) in long-COVID patients is underway. Combining quercetin with luteolin may provide additional benefits, especially when formulated in olive pomace oil (FibroProtek) that increases oral absorption, that is otherwise quite limited (<10%) [222]. Moreover, olive pomace oil provides additional antiviral [223] and anti-inflammatory [224]. Such liposomal preparations are available [222] and have been successfully used in pilot clinical trials [225] and reduced neuropsychiatric symptoms and associated serum IL-6 levels [226].

Conclusion

Further studies are urgently needed to address the neuropathogenesis of SARS-CoV-2 infection [227, 228] or the long-term effects of COVID-19 especially in the brain [229]. COVID vaccines have been enormously helpful [230–232], but there have been reports of rare neurological complications including Guillain-Barre syndrome and Bell’s palsy [233]. These may be related to the recent finding that the spike protein expressed in response to mRNA vaccines was detected in the circulation as early as 1 day post vaccination and became undetectable by day 14 [234]. Hence, we should try to limit or prevent spike-related detrimental effects especially to the brain and their potential contribution to the development of long-COVID.

Author Contribution Single author

Availability of Data and Materials Not applicable

Declarations

Ethics Approval Not applicable

Consent to Participate Not applicable

Consent for Publication Not applicable

Competing Interests The author is Scientific Director of Algonot LLC that develops flavonoid-containing dietary supplements.

Research Involving Human Participants and/or Animals Not applicable

Informed Consent Not applicable

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