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Marcos Altable *

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Link Between the G Protein-Coupled Receptor (GPCR), SARS-CoV-2 Spike Protein, ACE2, Vaccines, and Long COVID

Marcos Altable

Department of Neurology. Neuroceuta. (Virgen de África Clinic), Sargento Mena Street 4, 51001. Ceuta. Spain; maraltable@gmail.com; Id ORCID: 0000-0002-3849-4953

Abstract: The knowledge of COVID-19 impact on the human body has increased rapidly. Although many people recover from COVID-19, some continue to experience persistent symptoms that have been identified as Long COVID. This condition can have a severe impact on quality of life, and it remains a significant concern for medical professionals and researchers. One of the key components of the SARS-CoV-2 virus that enables it to enter human cells is the spike (S) protein. Recent studies have revealed a complex network of interactions between G proteins, spike (S) protein, and the Renin-Angiotensin System (RAS) may be responsible, at least in part, for long COVID. SARS-CoV-2 can also affect the brain, leading to neurological symptoms such as confusion, memory loss, and fatigue. Increasing evidence suggests that COVID-19 is not just a respiratory illness since it is likely that the virus could influence signal transduction pathways such as G-protein-coupled receptor (GPCR), among others, in the brain, either directly or indirectly, affecting neural functions. These interactions with the spike (S) protein and RAS, alongside the brain, are complex and require deep research to understand their implications for Long COVID-19 manifestation fully. While recent research has shed light on the complex interactions between G proteins, spike (S) protein, the brain, and the angiotensin system, this article explores these interconnected pathways and their implications for long COVID-19 manifestations. The present review summarises current research on different molecular mechanisms in Long COVID pathophysiology and may help identify possible targets or new strategies for the diagnosis and treatment.

Keywords: G protein-coupled receptor; SARS-CoV-2 spike (S) protein; vaccines; long COVID; ACE2; COVID-19

Introduction

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the causative agent of the COVID-19 pandemic. This has led to numerous scientific investigations to understand its pathophysiology, long-term implications, and modes of prevention. Among these studies, the role of the virus's spike (S) protein and its possible connection with the prolonged symptoms of COVID-19 is emerging as an area of interest. While many recover from the acute phase of the infection, a subset experiences persistent symptoms termed 'Long COVID' or 'Post-Acute Sequelae of SARS-CoV-2 infection' (PASC). Central to the biology of SARS-CoV-2 is the spike (S) protein, which facilitates viral entry into host cells [1–3]. As researchers delve into post-acute sequelae of SARS-CoV-2 infection (PASC) or Long COVID, questions have arisen regarding the role of the spike protein in these prolonged symptoms [1].

Multiple signalling pathways have been described in the pathophysiology of Long COVID, but the literature on the role of G-protein-coupled receptors (GPCRs) is very scarce. GPCRs are a large family of membrane-bound metabotropic receptors that play a role in many physiological processes, from responses to neurotransmitters and environmental stimuli to responses to hormones [4–6]. GPCRs have been demonstrated to interact with other critical physiological molecules, such as growth factors and their receptors, by generating transactivation signals that regulate cell motility. When a virus infects a host cell, it can use GPCRs as receptors to access the host cell, like the SARS-

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CoV-2 virus causing COVID-19 [6]. In contrast to ACE2 and Renin-Angiotensin System (RAS) mechanisms, GPCRs play a poorly understood role in COVID-19 and Long COVID pathophysiology.

The term Long COVID

Long COVID, also known as post-acute sequelae of SARS-CoV-2 infection (PASC), is a condition that affects individuals who have recovered from acute COVID-19 infection but continue to experience symptoms for weeks or even months after the initial infection. This condition is a multisystem syndrome that can affect various organs and systems in the body, including the respiratory, cardiovascular, neurological, and immune systems.

The symptoms of Long COVID are wide-ranging and vary in severity from person to person. Some common symptoms include fatigue, brain fog, difficulty concentrating, shortness of breath, chest pain, joint pain, muscle weakness, headaches, and loss of taste or smell. In some cases, Long COVID can also lead to more severe manifestations like myocarditis, pulmonary fibrosis, or chronic fatigue syndrome [3].

The exact mechanism behind long COVID remains unclear, but several hypotheses suggest that residual viral particles, immune dysregulation, or autoimmunity may play a role. It is also interesting to note that long COVID can occur in individuals who have had mild or even asymptomatic acute infections, indicating that the severity of the initial infection may not necessarily predict the likelihood of developing long COVID. Some studies have suggested that the spike protein of the SARS-CoV-2 virus may be implicated in the development of Long COVID. The spike protein is the part of the virus that allows it to enter human cells, and it has been shown to have several effects on the immune system and blood vessels that could contribute to Long COVID symptoms [7,8].

Long COVID currently has no recognised treatment, and investigations into the aetiology of the illness are still ongoing. However, healthcare providers are working to develop effective treatments and management strategies to help individuals with long COVID manage their symptoms and improve their quality of life.

Spike Protein and SARS-CoV-2 Entry

The spike protein of SARS-CoV-2 plays a crucial role in the virus's ability to infect human cells. This protein binds to the human angiotensin-converting enzyme 2 (ACE2) receptor, facilitating viral entry into host cells [2,3]. The protein's significance is also underscored by its central role in current vaccine strategies, which predominantly target the spike protein to elicit a protective immune response [7,8]. SARS-CoV-2 primarily infects human cells by utilising the angiotensin-converting enzyme 2 (ACE2) as its receptor. The primary entry mechanisms involve up to three steps.

Spike Protein and ACE2 Binding

The spike (S) protein of SARS-CoV-2 plays a vital role in viral attachment and entry into human cells. The receptor-binding domain (RBD) of the S1 subunit of the spike protein binds to ACE2 on the surface of human cells, particularly in the lungs [2].

Proteolytic Cleavage

After binding, the S protein undergoes proteolytic cleavage by host cell proteases, notably TMPRSS2 and furin. This cleavage, specifically at the S1/S2 and the S2′ sites, activates the spike protein for virus-cell membrane fusion [9].

Membrane Fusion

The S2 subunit of the spike protein mediates the fusion of the viral envelope with the host cell membrane, allowing the viral RNA to enter the host cell's cytoplasm. This step involves a series of structural rearrangements in the spike protein [10,11]. In addition to TMPRSS2-mediated entry, SARS-CoV-2 can also use an endosomal pathway for cell entry. After binding to ACE2, the virus is endocytosed and then requires the action of endosomal cysteine proteases, cathepsin B and L, for S

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protein activation and subsequent cell entry [11]. Fusing the viral envelope with the host cell membrane, mediated by the S2 subunit of the spike protein, is a critical step in viral entry into the host cell. This process involves a series of structural rearrangements in the S2 subunit. According to Su et al., these rearrangements include three hinges in the C-terminal base of the S2 subunit, which facilitate the capture of the host cell membrane and fusion with the viral envelope [12]. Conversely, Lipskij et al. contend that the S2 subunit does not undergo structural damage during this process, suggesting that such rearrangements may not be essential [13]. However, the involvement of structural rearrangements in the fusion process is supported by other studies. For example, Xu et al. describe the interaction of the S2 subunit with the natural surfactant film on the host cell membrane, inducing microdomain fusion in the surfactant monolayer due to membrane fluidisation caused by the insertion of the S2 subunit, mediated by its fusion peptide [14]. Niort et al. also elucidate that the repeated heptad domains of the S2 subunit bring the viral and cellular membranes close together while the fusion peptide interacts with and perturbs the membrane structure. This is facilitated by cholesterol and ceramide lipids from the cell surface, which aid in the membrane fusion process [15]. Furthermore, the formation of a six-helical bundle via the two-heptad repeat domain in the S2 subunit, as described by Huang et al., indicates significant structural rearrangements during the fusion process [16]. Hsu details that the structural rearrangements involve the spontaneous assembly of a trimeric complex, with heptad repeat 1 (HR1) antiparallelly surrounded by three heptad repeat 2 (HR2) to form a six-helical bundle, termed the fusion core [17].

ACE2: Distribution and Susceptibility to Infection

ACE2 is widely expressed in various human tissues. Thus, it is abundantly expressed in the epithelial cells lining the respiratory tract, especially in the alveolar type II cells in the lungs. This makes the lungs a primary site for SARS-CoV-2 infection and pathology [19]. ACE2 is also expressed in the upper oesophagus, small intestine enterocytes, and, to a lesser extent, in the colon. This may explain the gastrointestinal symptoms observed in some COVID-19 patients [20]. Moreover, it is present in the heart, especially in myocardial cells, which could contribute to cardiovascular complications in some COVID-19 patients [21]. ACE2 expression in the kidneys may make them a potential target for SARS-CoV-2 infection, which might contribute to acute kidney injury seen in some cases [22]. ACE2 is also found in various other tissues, including the testis, adipose tissue, and the central nervous system, suggesting these could also be potential sites of infection.

Diseases like hypertension, diabetes, and others may affect ACE2 expression, influencing susceptibility to infection and disease progression [24]. The widespread distribution of ACE2 in multiple organ systems suggests that while the respiratory system is the primary site of infection, SARS-CoV-2 can affect multiple organ systems. The expression of ACE2 is not the sole determinant of tissue susceptibility. Other factors, like the presence of proteases (e.g., TMPRSS2) that facilitate viral entry and innate immune responses, play crucial roles [9].

Different data have revealed that there are sex differences in ACE2 expression. In this sense, it has been observed that males might express higher levels of ACE2 in some tissues. Moreover, from an ontogenetic point of view, a decrease in ACE2 expression with age has been observed, which could explain, at least in part, differences in susceptibility and clinical outcomes over the years [21,23].

G Proteins and Their Role in Cellular Mechanisms

G proteins are guanine nucleotide-binding proteins that operate as molecular switches. In their inactive state, they are bound to guanosine diphosphate (GDP), but upon activation by G protein-coupled receptors (GPCRs), they bind guanosine triphosphate (GTP) [25]. G proteins, short for guanine nucleotide-binding proteins, serve as critical molecular intermediaries in cellular signalling pathways. These proteins play an essential role in numerous cellular processes, particularly in the transduction of signals from outside a cell to its interior. Understanding their structure and function provides insights into the complex web of intracellular responses to extracellular stimuli.

G proteins are heterotrimeric, meaning they are composed of three different subunits: α, β, and γ. The active and inactive states of G proteins are determined by the binding of guanosine

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triphosphate (GTP) or guanosine diphosphate (GDP) to the α subunit [26]. Several types of Gα proteins exist, each capable of activating different signalling routes: *Gαs* stimulates adenylate cyclase, which in turn increases cyclic AMP (cAMP) levels within the cell [26]; *Gαi* opposes Gαs by inhibiting adenylate cyclase, thereby reducing cAMP levels [27]; *Gαq* activates phospholipase C, leading to the generation of secondary messengers inositol trisphosphate (IP3) and diacylglycerol (DAG) [28]. They are implicated in multiple cellular mechanisms: signal transduction, cell cycle regulation, cell development, and differentiation [29–31].

In short, G proteins are versatile and essential molecular switches within cells, integral to numerous cellular processes. From receiving signals at the cell surface to activating intracellular pathways, G proteins ensure that cells can respond effectively to their environment.

G Proteins in the Brain

G proteins have a significantly pronounced role in the brain. They modulate myriad functions, from neurotransmission to cognitive processes, memory formation, and mood regulation [32]. The complexities of the brain, with its billions of neurons and even more synaptic connections, rely in part on the intricate dance of G protein signalling. Nevertheless, the role of G proteins in the brain extends far beyond simple cellular signalling. They are pivotal in orchestrating the symphony of neural processes that underpin cognition, emotion, behaviour, and the immune system. Comprehension of the intricacies of G protein functions in the brain holds promise for developing therapeutic strategies for various neuropsychiatric disorders.

Viruses can exploit G-protein-coupled receptors (GPCRs) as part of their entry mechanism into host cells. This process involves the virus hijacking the cellular signalling pathways mediated by GPCRs, which are crucial for a variety of physiological functions, including immune responses. GPCRs, by interacting with various ligands and undergoing conformational changes, play a pivotal role in the regulation of T-cell activity and immune system modulation. This interaction is crucial for the identification and neutralisation of pathogens, including viruses. Additionally, the signalling cascades triggered by GPCRs, involving proteins like Gq/11, contribute to regulating intracellular calcium levels and other signalling molecules, which are essential for viral entry and cell replication [33].

GPCRs play a significant role in regulating T-cell immunity, as highlighted by various studies. Research has identified an enrichment of Gαs-coupled GPCRs on exhausted CD8+ T cells across various cancer types, indicating their involvement in T cell dysfunction and potential failure of cancer immunotherapies. GPCRs like EP2, EP4, A2AR, β1AR, and β2AR are associated with promoting T-cell dysfunction. The Gαs-PKA signalling axis, in particular, has been shown to contribute to CD8+ T cell dysfunction, suggesting that Gαs-GPCRs could serve as druggable immune checkpoints to enhance responses to immune checkpoint blockade (ICB) therapies [34].

Another study further emphasises the critical role of GPCRs in T-cell immunity and delves into their involvement in key cellular and physiological processes. It showed that GPCRs, activated by a wide range of ligands, including neurotransmitters and chemokines, are integral to sense perception, neurotransmission, metabolism, and various secretion processes. Their principal role extends to the immune system, significantly impacting T-cell activation, homeostasis, and overall function [35]. This underscores the essential nature of GPCR signalling in maintaining and regulating T cell-mediated immunity.

Likewise, G proteins play a central role in the modulation of neurotransmitter release. Specific GPCRs inhibit the release of neurotransmitters via Gi proteins, while others stimulate release via Gs proteins [27]. Likewise, G proteins are involved in processes of sensitisation and desensitisation of neurotransmitter receptors. This is essential for synaptic plasticity. Neuroplasticity refers to the brain's ability to reorganise itself. G proteins have been implicated in various forms of synaptic plasticity, including long-term potentiation (LTP) and long-term depression (LTD), critical processes behind cognition, learning and memory [36,37]. It might provide therapeutic options, as modulation of GPCR signalling could affect viral replication and host inflammatory responses [10].

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G Proteins and Neuropsychiatric Disorders

Abnormalities in G protein signalling, which is a complex process that regulates various cellular functions in the brain, can lead to a range of neurological and psychiatric disorders. Research has shown that these abnormalities can affect the functioning of neurotransmitters, ion channels, and other signalling molecules in the brain, which can ultimately lead to impaired cognitive, motor, and emotional processes. Some of the brain disorders that have been linked to G protein signalling abnormalities include schizophrenia, depression, bipolar disorder, Parkinson's disease, and addiction.

Alterations in G protein functions can affect monoaminergic neurotransmission, commonly associated with mood disorders [38]. These alterations play a significant role in the regulation of monoaminergic neurotransmission, with implications for mood disorders such as depression and bipolar disorder [38]. The impact of these alterations on α2A-adrenoceptors shows increased sensitivity in the frontal cortex of suicide victims with mood disorders, which underscores the involvement of α2-adrenoceptors in the pathogenesis of these conditions [39]. Furthermore, the same authors suggest that changes in signal transduction through GPCR pathways may contribute to the development of mood disorders and associated suicidal behaviour [40]. It has been proposed that probiotics, which release neurotransmitters including GABA, serotonin, noradrenaline, acetylcholine, and dopamine, interacting with GPCRs, could offer innovative treatments for mood disorders linked to alterations in G protein functions [41]. These changes, mainly through the kappa opioid receptor (KOR), regulate serotonin and dopamine transporters, which are crucial in aminergic neurotransmission and affect mood and addiction, linking G protein alterations to mood disorders [42]. Regarding the roles of inflammation, reward and threat circuitry, and neurotransmitter systems in how altered G protein functions contribute to mood disorders, these factors mediate the impact on monoaminergic neurotransmission [43]. The control of the Wnt pathway is connected to these neuroinflammation alterations, where microglia regulate neurotransmitter synthesis and immune cell activation in bipolar disorder [44].

Changes in the auxiliary subunit KCTD12 of GABAB receptors, associated with mood disorders, can increase fear learning and the intrinsic excitability of hippocampal pyramidal neurons, highlighting the complex relationship between G protein functions and mood regulation [45]. The neuromodulatory effects of teneurins and latrophilins, influenced by G protein interactions, on neuronal structure and behaviour, further connecting G protein alterations to mood disorders [46]. In resume, these studies indicate that alterations in G protein functions can significantly impact monoaminergic neurotransmission, contributing to the pathophysiology and potential treatment avenues for mood disorders such as depression and bipolar disorder.

Some studies suggest abnormalities in G protein signalling pathways in the brains of individuals with schizophrenia [39]. Evidence suggests abnormalities in G protein signalling pathways in the brains of individuals with schizophrenia, impacting the development, progression, and treatment of the disease. GPCRs have been implicated in the pathophysiology of schizophrenia [47]. The Reelin signalling pathway, associated with schizophrenia, involves components such as Reelin receptors, Src family kinases, and the intracellular adaptor Dab1, suggesting disruptions in G protein-related signalling [48]. Alterations in the activity of protein kinase A (PKA), a component of the cAMP-associated pathways, have been observed in the frontal cortex of individuals with schizophrenia, indicating anomalies in G protein signalling [49]. Protein misfolding and aggregation in psychiatric disorders, including schizophrenia, involve proteins like DISC-1 and SNAP25, which may relate to G protein pathway dysfunction [50].

Abnormal phosphorylation of cAMP-response element binding protein (CREB) by dopamine via GPCRs in schizophrenia highlights the role of G protein signalling alterations, with certain genetic variants of CREB found only in schizophrenic patients [51]. Moreover, abnormal activity in MAPK- and cAMP-associated signalling pathways in the frontal cortical areas of the brain has been documented in schizophrenia [52]. Evidence also points to selective increases in phosphoinositide signalling activity and G protein levels in specific frontal cortex regions in schizophrenia, suggesting localised abnormalities in G protein pathways [53]. Furthermore, alterations in G protein signalling,

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especially involving the RGS4 gene and mRNA levels of various RGS proteins, have been implicated in schizophrenia, indicating a complex relationship between G protein signalling and the disorder [54,55].

G proteins and their downstream effectors are crucial in neural circuits modified by drug addiction [40]. G proteins and their downstream effectors play a pivotal role in neural circuits affected by drug addiction, although the specifics of these modifications and mechanisms are not fully elucidated [56]. Studies indicate that addiction alters the function of proopiomelanocortin (POMC) and agouti-related peptide (AgRP) neurons within the central melanocortin system, which, along with the mesolimbic dopamine system, regulates reward-related behaviours in drug use [57]. Complexes formed by mGlu5 receptors with other GPCRs, such as adenosine A2A and dopamine D2 receptors in the striatum, a critical region in drug addiction, may influence drug-seeking behaviours and the rewarding effects of drugs. This suggests potential avenues for drug discovery aimed at reducing side effects [58]. The β-arrestin arm of β-adrenergic signalling is implicated explicitly in promoting extinction learning of cocaine reward memory, suggesting that enhancing β-arrestin signalling in the infralimbic prefrontal cortex might help prevent relapse in cocaine addicts [16]. G proteins and their downstream pathways, notably Epac2, are crucial in cocaine-induced changes in AMPA receptor subunit composition in the ventral tegmental area, linked to drug-cue associative learning and addiction [57]. Additionally, activation of Activin signalling, which increases Activin receptor 2a (ACVR2a) and phosphorylation of SMAD3 in neurons of the nucleus accumbens (NAc), leads to an increase in dendritic spine density on NAc medium spiny neurons, contributing to cocaine self-administration and relapse [59].

RAS and its Implications in the Brain

RAS is a complex system that plays a crucial role in regulating blood pressure and fluid balance. It involves a series of enzymatic reactions that ultimately lead to the production of angiotensin II (Ang II), a potent vasoconstrictor that binds to the AT1R receptor and affects various processes, including inflammation, oxidative stress, and cellular growth. Interestingly, RAS components also exist in the brain and have been found to influence neural activities, including cognitive processes, stress response, and thirst sensation. Studies have shown that Ang II can cross the blood-brain barrier and activate AT1R receptors in various brain regions, including the hypothalamus, amygdala, and hippocampus. This activation can lead to the release of neurotransmitters such as norepinephrine and dopamine, which are involved in regulating mood, cognition, and behaviour. In addition, RAS in the brain has been implicated in the development and progression of various neurological disorders, including Alzheimer's disease, Parkinson's disease, stroke, and Type 2-induced dementia, together with glaucoma and diabetic retinopathy [60].

It discussed the potential of small molecule agonists and inhibitors of RAS components as treatments for these disorders [61]. Additionally, they note the role of the angiotensin IV/AT4 receptor subtype system within the RAS in regulating neuronal firing rate, long-term potentiation, and learning and memory, which may contribute to memory-related neurological disorders [60]. Angiotensin receptor blockers (ARBs) can improve cerebrovascular blood flow, reduce brain injury factors, and activate the PPARγ mechanism, suggesting their development potential for treating various neurological disorders [61]. Given the role of ACE2 in viral entry, strategies that inhibit the binding of the S protein to ACE2 might be therapeutically beneficial. Drugs targeting the RAS, including ACE inhibitors and angiotensin receptor blockers (ARBs), are being investigated for potential protective roles in COVID-19 patients, but conclusive evidence is yet to be provided [48]. ARBs have been found to modulate ACE2 expression and could potentially provide a protective effect in COVID-19 patients [47,48]. More studies are needed to understand the mechanisms underlying these potential therapies and to determine their clinical efficacy in treating COVID-19.

Briefly, RAS is a fascinating and complex system that plays a crucial role in regulating various physiological processes in the body and brain. Understanding its intricacies may lead to new insights and therapies for various diseases and conditions.

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The Intricate Relationship between G Proteins, RAS, Spike Protein, and Brain in Long COVID

GPCRs play a role in some of the effects of Ang II in the brain, indicating a convergence of G protein and RAS pathways in neurophysiological processes [62]. The interaction between these two systems may be disrupted in neurological conditions such as Alzheimer's disease and depression. However, more research is needed to determine the exact mechanisms involved [63]. GPCRs are known to mediate some of the effects of Ang II in the brain, which suggests that there is a convergence of G protein and RAS pathways in neurophysiological processes [62]. However, dysregulation of these intertwined systems may contribute to neurological conditions such as Alzheimer's disease and depression. The primary route of entry for SARS-CoV-2 into human cells is through the ACE2 receptor, which plays an essential role in modulating the RAS [9]. The virus binds to ACE2, which leads to its internalisation into the host cell, where it can replicate and cause damage. Neurological symptoms such as loss of smell (anosmia) and severe encephalopathy have been reported in COVID-19 patients, indicating potential interactions between the virus and the RAS and G protein pathways in the brain [64]. These interactions may play a role in the development of neurological symptoms and require further investigation to better understand their mechanisms. Increasing evidence suggests that COVID-19 is not just a respiratory illness. While direct evidence remains limited, it is conceivable that the virus could influence GPCR signalling in the brain, either directly or indirectly, affecting neural functions [65].

GPCRs may affect the immune response to viral infections, including SARS-CoV-2. While GPCRs, including those associated with Protein G, have been studied in the context of various viral infections (including respiratory syncytial virus), their direct role in the context of SARS-CoV-2 remains less explored [65]. However, it has been described that G-protein-coupled receptors (GPCRs) allow viruses to enter and infect host cells [6].

Approximately half of the over 800 human GPCRs are sensory receptors that regulate olfaction, light perception, and pheromone signalling. More than 90% of the remaining non-sensory GPCRs, numbering over 370, are expressed in the brain and mediate communication from a variety of ligands, thereby regulating various physiological processes throughout the human organism, primarily endocrine and neurological functions. GPCRs are the most used therapeutic drug targets [67]. At the subcellular level, Gi/o-coupled GPCRs can be detected and analysed for functions such as neurite outgrowth, neurotransmitter release, and synaptic plasticity, which are then processed into complex brain processes such as memory, learning, and cognition. Serotonin, dopamine, cannabinoid, and metabotropic glutamate receptors enhance short-and long-term memory, memory consolidation, and learning. Most GPCRs, encompassing dopamine, serotonin, and opioid receptors, are essential in modulating and affecting behaviour and emotions. GPCR signalling is also crucial for sleep and circadian rhythm regulation [68].

Connecting the Spike Protein and Long COVID

There is ongoing research into the relationship between the S protein and Long COVID, and several hypotheses have been proposed. Some scientists believe that the S protein, which is found on the surface of the COVID-19 virus, may play a role in the development of Long COVID symptoms. One hypothesis suggests that the S protein may trigger an autoimmune response in some people, leading to long-term inflammation and other symptoms. Another hypothesis proposes that the S protein may directly damage cells in the body, causing long-lasting effects. More research is needed to fully understand the relationship between the S protein and long COVID.

Potential Persistent Infection

Some scientists have suggested that residual viral particles, which may be present in low quantities or inactive, could persist in specific tissue reservoirs or sanctuaries, continually triggering symptoms in long COVID patients [69–71]. These particles, particularly those containing the spike protein, could stimulate an ongoing immune response, leading to tissue damage and the diverse symptoms associated with Long COVID. However, more research is required to confirm this theory.

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If true, it could have significant implications for the management and treatment of Long COVID, as well as for our understanding of the virus's long-term effects on the body. It is necessary to examine the role these residual viral particles play and how they contribute to the symptoms experienced by Long COVID patients.

Autoimmune Responses

Some studies suggest that SARS-CoV-2 might trigger an autoimmune response in certain individuals. Given that the spike protein is at the viral forefront during infection, it is plausible that it could be involved in eliciting such responses, where the immune system begins to target the body's cells [72–75]. This molecular mimicry between viral proteins and host proteins, including protein S, could trigger autoimmune reactions and explain some persistent symptoms in patients with Long COVID. According to some studies, there is evidence to suggest that SARS-CoV-2 could potentially cause an autoimmune response in specific individuals. As the immune system tries to fight off the virus, it may start to target its own cells in the process, leading to an autoimmune response. This autoimmune response could be triggered by molecular mimicry, where viral proteins such as protein S have a similar structure to human proteins. This similarity could cause the immune system to mistake the cells for the virus, leading to an attack on the body's healthy tissues. This could also explain some persistent symptoms experienced by patients with Long COVID, such as fever, fatigue, and joint pain. Further research is still needed to better understand the relationship between the spike protein and autoimmune responses in COVID-19 patients. However, this new information is a crucial step in identifying potential treatments for patients with autoimmune disorders triggered by the virus.

Role of Vaccines

Receipt of vaccination with either an mRNA or adenoviral vector vaccine was not clearly associated with a worsening of long Covid symptoms, quality of life, or mental well-being.

A study from the COVID-19 Infection Survey explored this by examining the effects of vaccination on individuals previously infected with SARS-CoV-2. It showed that the likelihood of long COVID-19 symptoms decreased after COVID-19 vaccination, and evidence suggested sustained improvement after a second dose, at least over the median follow-up of 67 days. Vaccination may contribute to a reduction in the population health burden of long COVID [76,77].

Besides, another study concluded that receiving vaccination with either mRNA or adenoviral vector vaccine was not associated with a worsening of long COVID-19 symptoms, quality of life, or mental wellbeing. Individuals with prolonged COVID-19 symptoms should receive vaccinations as national guidance suggests [78].

Although the connection between the spike protein and long COVID is still being researched, understanding this relationship can provide valuable insights into potential treatments and preventive measures for long COVID. It is essential to stay up-to-date with the latest research findings to get a complete understanding of the ongoing pandemic and its long-term implications.

Current COVID-19 vaccines are primarily designed to generate an immune response against the spike protein. While some may worry that vaccines could trigger symptoms similar to long COVID because of this targeting, current evidence suggests that vaccines are safe and may even help reduce long COVID symptoms in some individuals.

Conclusion

It is worth highlighting the importance of understanding SARS-CoV-2's spike (S) protein concerning COVID-19 and its prolonged symptoms, often termed 'long COVID' or 'Post-Acute Sequelae of SARS-CoV-2 infection' (PASC). The S protein is central to the virus's entry into host cells and is a key target for current vaccine strategies. Long COVID is characterised by persistent symptoms that can last weeks to months after the initial infection, affecting even those with mild or

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asymptomatic cases. The exact mechanisms behind Long COVID are unclear, but theories include residual viral particles, immune dysregulation, and the potential role of the spike protein.

The spike protein facilitates SARS-CoV-2 entry into human cells by binding to the ACE2 receptor, undergoing proteolytic cleavage by host proteases like TMPRSS2, and mediating membrane fusion. ACE2's wide distribution in various human tissues explains COVID-19's multi-organ effects. Factors such as age, gender, and pre-existing conditions can influence ACE2 expression and susceptibility to infection.

The connection between the spike protein and Long COVID includes theories of persistent infection where residual viral particles, including the spike protein, might trigger ongoing symptoms. Additionally, an autoimmune response triggered by the spike protein could contribute to Long COVID symptoms. While concerns exist about COVID-19 vaccines, which target the spike protein, potentially exacerbating Long COVID, current evidence suggests vaccines are safe and may reduce symptoms in some individuals. Understanding the role of the spike protein in Long COVID is crucial for developing treatments and preventive measures. The intricate dance between G proteins, the brain, and RAS offers a lens through which we can view some of the multifaceted effects of COVID-19. It is known the implication of G proteins in neuroinflammation, neurotransmission and neuroplasticity, which may explain the neurological and neuropsychiatric manifestations observed in Long COVID. As our understanding grows, so will the potential for targeted interventions that leverage knowledge of these interconnected systems. Additional research is needed to fully understand the implications of these interactions for the long-term manifestations of COVID-19.

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