Review Article

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Investigating the Role of Serotonin Levels in Cognitive Impairments Associated with Long COVID-19

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This study aimed to investigate the activation of the inflammation process, triggered as an immune response to combat the invasion by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is a highly transmissible and pathogenic coronavirus that emerged in late 2019 and has caused a pandemic of acute respiratory disease, named 'coronavirus disease 2019' (COVID-19). Several mechanisms contribute to the reduction in serotonin levels, such as the impaired absorption of dietary tryptophan, hindered serotonin transport via platelets, and increased activity of an enzyme responsible for breaking down serotonin. Individuals seeking treatment for long COVID-19 had lower serotonin levels in their blood than those who had fully recovered from the infection. Furthermore, patients with long COVID-19 also had reduced tryptophan levels. The potential benefits of dietary supplementation with tryptophan or the use of selective serotonin reuptake inhibitors (SSRIs) to improve cognitive impairments and depressive and anxiety disorders in long-term COVID-19 patients. The findings support the immune response's pivotal role in modulating serotonin levels and further highlight the intricate connection between the immune system and neurotransmitter regulation.

Key Words: *Immune System; Nervous System; Serotonin; SARS-CoV-2; COVID-19*

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INTRODUCTION

COVID-19 is a respiratory infectious disease caused by a pathogen closely linked to the SARS coronavirus. The causative virus of COVID-19 disease.[1] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly transmissible and pathogenic coronavirus that emerged in late 2019 and has caused a pandemic of acute respiratory disease.[2] Based on the study in 2022, the prevalence of COVID-19 was estimated at 1.07% and the cumulative incidence rate was 9.26 cases per 100 person-years.[3] There is heterogeneity in the long-term complications seen following COVID-19. The most common symptom reported following COVID-19 are dyspnea,[4] cardiac injury,[5] hypercoagulability,[6] neurological and psychiatric disaster,[7] maculopapular exanthema,[8] hyperglycemia,[9] acute kidney injury,[10] gastrointestinal[11] and musculoskeletal symptoms,[12] and male infertility.[13]

The immune system and the nervous system of our bodies have remarkably similar roles at the cellular level by playing very vital roles. Further, there is an intricate manner in which they intertwine to create a two-way interaction in their communication and coordination approaches which then ensures the body functions optimally at all times, thereby preserving an equilibrium state – a principle that's echoed in several research studies.[14,15] Once thought of merely as the body's defense squadron against foreign entities, deeper insights have revealed that the immune system can perhaps be best understood as a high tech sensory organ. What makes the immune system an extraordinary organism within the human body is its eminent capability to perceive and gather unique information using various chemical mediators. Not only it is this data collection effective, but it has also proven essential over time. Another fantastic capability of the immune

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system that cannot be overlooked is its unique ability to recognize and appropriately respond to different signals such as harmful bacteria and attacks from viruses; sometimes these threats are even too shifty and evasive for an advanced intricate nervous system to recognize. And much to our - perhaps our nervous system's - relief, our immune system stands guard at all times, to keep these evils at bay, revoking their advances largely unnoticed, but decisively succinct. This attribute allows it to maintain general health and plays a crucial role in preserving the wellness of the body. Such an ability, as researchers propose, explains how the immune system upholds an array of directive and life-preserving functions.[16] Looking into the essential and noteworthy attributes of the Coronavirus disease 2019 (COVID-19) from a pathophysiological perspective, it is indeed important that we turn our focus and efforts towards analyzing and understanding one remarkable feature: the commencement and progression of the inflammatory cascade. It is pertinent not to overlook this aspect and ensure it gets the attention and analysis it truly merits. When you scrutinize the situation, you'll likely realize the extent to which starting this complex chain of responses can have a plausible potential in causing malfunctions in essential organs throughout our bodies. Not just limited to singular organ impact, these impairments include in number and significance, the far-reaching effects of disrupted functionality of the brain--a highly intricate and delicate structure within the human anatomy.[17] Among the various neurotransmitters that exist within the intricate and complex human body, serotonin, a significant and pivotal neurotransmitter, assumes crucial and indispensable functions in the immune system, thereby exerting its influence through a combination of both central and peripheral mechanisms, contributing to the overall maintenance and regulation of this highly intricate system responsible for safeguarding the body against harmful pathogens and maintaining its internal equilibrium.[18]

SEROTONIN AND COGNITIVE SYMPTOMS IN LONG COVID-19

For a long time, significant relationships have been drawn linking the pathophysiology of depressive disorders to serotonin and norepinephrine, which are rather well-known biogenic amines. However, they're not the only nuggets of importance in this scenario as the inhibitory signal-oriented neurotransmitter called GABA, also takes center stage and draws just as much attention. The prestigious trio of vital neurotransmitters, lovely serotonin, essential norepinephrine, and incredibly significant GABA, have all found themselves under the scrutiny of rigorous examination, mainly due to their suspected correlation with various anxiety disorders.[19] When it comes to examining the underlying factors contributing to anxiety levels, serotonin, among other brain chemicals such as norepinephrine and GABA, plays an absolutely critical role, one too important to overlook. By diving into this topic, extremely interesting observations have surfaced. Specifically, it's been determined that those poor souls who suffer from overarching, traumatic stress often display lower-than-average levels of serotonin regularly. Constantly low concentrations of this significant chemical in the brain often underpin a series of notably diverse symptoms. These may typically include anhedonia, that notorious inability to feel pleasure, an engulfing sense of apathy, weaknesses in focusing attention and even manifesting as tangible motor deficits. It's like a cascade of daunting issues, all unfolding due to a deficiency in this pivotal chemical compound in the brain.[20-22] When the immune system is constantly alerted or stimulated, like when a viral infection is present for example, this could lead to something more serious called chronic inflammation. Because the immune response fails to rid the body of the viral infection promptly, an aggressive reaction from the immune system ensues causing it to degrade tissues and produce auto-antibodies. All engraved in this exacerbated immune response are potentially destructive elements, making it a consorting catalyst to the progression of numerous diseases. Being left to fester in the body overtime, an uncontrollable immune response to viral infections can cause significant tissue damage and for the body to turn on itself by creating auto-antibodies. Through infecting the foundation of various disease pathogeneses, a relentless and muddled response brought forth by an untreatable viral illness exhibits the imperatives of a well maintained immune response.[23]

LONG COVID-19 AND COGNITIVE SYMPTOMS

Long COVID-19 refers to the persistent symptoms experienced by individuals even after they have recovered from the acute phase of Covid-19. These symptoms can include difficulty concentrating, problems with attention and memory, and other cognitive impairments that significantly affect daily functioning.[24] While the exact mechanisms underlying these cognitive symptoms in Long COVID-19 are not yet fully understood, recent research has proposed a link between inflammation in response to SARS-CoV-2 and a reduction in serotonin levels.[25,26] Serotonin is a crucial chemical messenger involved in regulating mood, digestion, and various other functions in the body.[27]

Inflammation caused by SARS-CoV-2 can lead to a drop in serotonin levels, which, in turn, may result in cognitive problems. The researchers observed that individuals seeking treatment for Long COVID-19 had lower serotonin levels in their blood compared to those who had fully recovered from the infection. Even acute Covid-19 patients showed reduced blood serotonin levels.[28]

The study identified several mechanisms that contribute to the reduction in serotonin levels. Firstly, viral infection or inflammation hindered the absorption of dietary tryptophan in the mouse gut. Tryptophan is a precursor of serotonin found in various foods.[29] Secondly, it impaired the transport of serotonin via platelets in the bloodstream. Lastly, it increased the activity of an enzyme responsible

for breaking down serotonin.[30,31]

MECHANISMS OF THE DROP IN SEROTONIN

Recent theories propose that alterations in the synthesis pathways of both dopamine and serotonin could contribute to the pathophysiology of COVID-19.[32] This potential involvement of these neurotransmitters is supported by a significant link – based on similarities related to gene co-expression, co-regulation and function – between Angiotensin I Converting Enzyme 2 (ACE2), which encodes the primary receptor for SARS-CoV-2 and Dopa Decarboxylase (DDC) which encodes the enzyme responsible for producing dopamine, serotonin, and histamine. Evidence indicates that ACE2 and DDC co-express and co-regulate within non-neuronal cell types. Additionally, ACE2 receptors are found to be highly expressed in dopamine neurons, and their levels are diminished in Parkinson's disease, a condition marked by dopamine deficiency.[33] Therefore, reduced expression of ACE2 induced by SARS-CoV-2 may be associated with dysfunction of DDC, potentially leading to altered neurotransmitter levels in COVID-19 patients.[32] It has also been suggested that SARS-CoV-2 may utilize the dopamine receptor as an additional point of entry.[34]

Moreover, it has been experimentally proven that the occurrence of viral infections, followed by an excessive release of pro-inflammatory cytokines, commonly known as cytokine storm, can play a significant role in diminishing the levels of serotonin and melatonin, two important neurotransmitters and hormones, respectively, that are crucial for various physiological and psychological processes in the human body.[35]

An effective immune response against SARS-CoV-2 necessitates the involvement of both the innate and adaptive immune systems. The innate immune system, which includes granulocytes, monocytes, and macrophages, collaborates with the adaptive immune system, comprising T and B cells.[36] While the mechanisms of viral entry for SARS-CoV-2 are well understood, subsequent steps remain unclear. The specific pattern recognition receptors (PRRs) that recognize SARS-CoV-2 have yet to be definitively identified. Based on research from other coronaviruses, the primary candidates are Toll-like receptors 3 (TLR3) and TLR7, which are located in the endosome, as well as cytosolic sensors like retinoic acid-inducible gene 1 (RIG-I) and melanoma differentiation-associated gene 5 (MDA5), which detect the RNA of foreign viruses.

These PRRs are connected through signaling pathways that trigger strong interferon responses. Growing evidence suggests that SARS-CoV-2 targets the type I interferon system at multiple levels, significantly disrupting the coordinated interaction between antiviral and pro-inflammatory innate and adaptive immune responses. Transcriptomic analyses of blood-derived cells have validated the bioactivity of certain inflammatory mediators, particularly IL-6 and TNF, showing elevated response signatures in circulating immune cells. In this hyper-inflammatory condition, inflammatory cell death has been linked to elevated levels of TNF and (interferon γ) IFNγ, which can initiate pyroptosis, apoptosis, and necrosis (collectively referred to as PANoptosis), leading to tissue damage and increased mortality in severe COVID-19 cases. Additionally, the simultaneous upregulation of IFNγ and IL-10, especially with higher IFNγ levels in mild cases, is a notable characteristic of COVID-19.[37]

Reduced levels of serotonin, a neurotransmitter known to regulate mood and emotions, were found to be associated with an increased activity of IFN I signaling, a key player in the immune response against viral infections. This heightened IFN signaling is commonly observed during viral responses, where the immune system recognizes and mounts a defense against invading viral pathogens. Interestingly, by inhibiting this specific pathway or targeting the components responsible for sensing viral RNA, researchers were able to prevent the reduction of serotonin levels. Additionally, serotonin has been proposed to have either stimulating or inhibiting effects on immune cells, including T cells, B cells, natural killer cells, and monocytes/macrophages.[38] Also, the pro-inflammatory cytokines further reduce the availability of monoamines, such as serotonin, by increasing the expression and function of the presynaptic reuptake pumps.[39] A significant portion of the mood and anxiety symptoms triggered by IFN-alpha can be mitigated by pre-treating with selective serotonin reuptake inhibitors (SSRIs), suggesting that these symptoms may be linked to the impact of cytokines on serotonin metabolism.[40] On the other hand, inflammatory cytokines have been shown to enhance the expression and activity of reuptake pumps (transporters) for serotonin, norepinephrine, and dopamine by activating signaling pathways, including mitogen-activated protein kinase (MAPK) pathways such as p38 MAPK.[41]

This finding provides strong evidence supporting the pivotal role of the immune response in modulating serotonin levels and further highlights the intricate connection between the immune system and neurotransmitter regulation.[42]

REVERSING THE IMPAIRMENT

Interestingly, the impairment in memory and cognitive function could be reversed. Supplementation of the mice's diet with tryptophan or administration of an antidepressant called fluoxetine, which boosts serotonin levels in the brain, improved their performance on memory tests and restored hippocampal activity.[43,44] However, it's important to note that the study mainly relied on experiments conducted in mice, raising some questions about its direct applicability to humans. Theoretical considerations and preliminary experimental findings indicate that a highly active kynurenine pathway, along with decreased production of serotonin and catecholamine neurotransmitters may be linked to symptoms of mental stress, anxiety and depression in patients with COVID-19. However, the relationship

between mental health, inflammation, kynurenine and catecholamine pathway activity and systemic levels of serotonin and dopamine in COVID-19 has not been explored in clinical groups.[45] It has been proposed that the potential depletion of tryptophan through the kynurenine pathway might restrict systemic serotonin availability in an inflammatory context.[46] Additionally, IL-6 has been recognized as a factor that may predict lower plasma serotonin levels.[47]

Liu et al.[48] determined the impact of phototherapy on neurotransmitters (BH4, BH2, and tryptophan) and behavioral neuroinflammatory responses in individuals with post-stroke depression. The study found that phototherapy significantly influenced the metabolism of BH4, BH2, and tryptophan, as well as behavioral neuroinflammatory responses and the overall quality of life for these patients. By enhancing the secretion and synthesis of neurotransmitters, phototherapy effectively modulated neuroinflammatory responses, improved biochemical indicators, increased antioxidant capacity, and relieved symptoms of depression.[48] Furthermore, Hebbrecht et al.[49] found that patients with bipolar depression have significantly lower plasma levels of tryptophan than healthy controls. In individuals with major depressive disorder (MDD) and a history of suicidality, a higher KYN/TRP ratio (characterized by elevated kynurenine levels and reduced tryptophan levels) has been observed compared to those without such a history or to healthy controls.[50] The understanding of how serotonin exerts its neurocognitive effects and how it relates to Long COVID-19 symptoms in humans need further studies.

THE RELEVANCE TO LONG COVID-19

Despite the limitations, the study's findings provide valuable insights into the potential link between serotonin and cognitive symptoms in Long COVID-19. The researchers discovered that patients with Long COVID-19 also had reduced tryptophan levels in their blood. Additionally, the analysis of stool samples revealed the presence of SARS-CoV-2 RNA in some patients, suggesting that the virus might persist in the digestive tract and interfere with tryptophan absorption.[51] However, some researchers caution that the connection between peripheral serotonin (circulating outside the brain and spinal cord) and cognitive symptoms in Long COVID-19 remains unclear.[52] Reduced peripheral serotonin alone may not fully explain the complex range of symptoms experienced by patients. Nevertheless, the finding of reduced tryptophan levels is intriguing and may have relevance to understanding Long COVID-19.

CONCLUSION

This study highlights the significant role of the inflammatory process, activated as an immune response to SARS-CoV-2, in influencing serotonin levels in patients affected by COVID-19, particularly those with long COVID symptoms. The findings indicate that mechanisms such as impaired dietary tryptophan absorption and increased serotonin breakdown may contribute to reduced serotonin and tryptophan levels in these individuals. This reduction in serotonin is associated with cognitive impairments and mood disorders in long COVID-19 patients. The potential benefits of dietary tryptophan supplementation and the use of SSRIs suggest promising avenues for alleviating these psychological symptoms. Overall, the study underscores the complex interplay between the immune system and neurotransmitter regulation, with implications for therapeutic strategies to improve the mental health of those suffering from the long-term effects of COVID-19.

FUTURE PERSPECTIVE

Scientists are currently hoping to implement clinical assessments to delve into examining if including tryptophan in diets or utilizing Selective Serotonin Reuptake Inhibitors (referred to as SSRIs), such as Fluoxetine, can effectively enhance and address cognitive impairments noticed in patients that continue to present COVID-19 symptoms over a long-term period, frequently referred to as Long COVID-19 patients. That said, the primary concern is to figure out which specific groups of these patients would gain significant benefit from such medical interventions; given that Long COVID-19 cases are manifold and hold diverse types propelled by varying underlying causations. It is rather important to underscore that in its essence, Long COVID-19, is not a simple ailment but an amalgamation of an intricate medical condition that is orchestrated by multiple origins and factors. While reduced serotonin levels may define one specific type, more work is required to fully understand how this reduction in serotonin contributes to cognitive symptoms. Clinical trials focusing on individuals with lower-than-normal serotonin levels could provide valuable insights into the potential benefits of SSRIs in Long COVID-19.

CONFLICT OF INTEREST STATEMENT

None declared.

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