



## Review article

The relationship between the serotonergic system and COVID-19 disease:  
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## ABSTRACT

COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which led to a pandemic started in Wuhan, China, in 2019. The rapid spread of the disease in the world, unprecedented mortality rate, and lack of definitive treatment for the disease have led to a global effort to develop effective vaccines as well as new therapeutic interventions. Immune cells activation with excessive inflammation is an important pathophysiological feature of COVID-19 that may impair the various organs functions. Accordingly, these could cause dysfunction in the brain with some symptoms such as respiratory failure, headache, impaired consciousness, olfactory and taste disorders, and severe neurological disorders such as encephalitis. It was found that there is a two-way communication between the immune system and the nervous system through classical neurotransmitters, hormones, and cytokines. Among neurotransmitters, serotonin plays important roles in the immune system and in regulating inflammatory responses by central and peripheral mechanisms. This article aimed to review the two-way relationship between the immune and the nervous systems by focusing on the serotonergic system and the emerging COVID-19 disease.

## 1. Introduction

It was previously believed that the immune system and the nervous system are two completely separate systems and follow different strategies in the body. However, later, it was found that these systems' functions are quite similar at the cellular level. In the immune system, cells communicate with each other even with a distance, exchange signals that are similar to the nervous system, the information of which is transmitted between neurons in different parts of the body. Besides having similarity in behaviors, there is growing evidence that these systems also have overlapping strategies in the body. In other words, a two-way interaction exists between these two systems in the body [1, 2, 3, 4, 5].

Bilateral communication between these two systems is created by binding classical neurotransmitters such as serotonin or 5-hydroxytryptamine (5HT), catecholamines, acetylcholine (ACh); hormones such as oxytocin; and cytokines such as interleukin-1 (IL-1) and tumor necrosis factor (TNF) to receptors in the immune system, nervous systems, and endocrine system. On the other hand, immune cells produce neuropeptides and neurotransmitters independently. For example, lymphocytes produce peptide hormones and neurotransmitters such as, 5-HT, ACh, and endorphins. It is noteworthy that various diseases such as multiple

sclerosis, Alzheimer's, and other neurodegenerative diseases are resulted from such a two-way relationship [6, 7, 8, 9, 10]. The immune system can be considered as a sensory organ that receives and processes certain information via chemical mediators and detects stimuli including bacteria and viruses that are not recognizable by the nervous system [11].

Coronavirus disease 2019 (COVID-19) started in Wuhan, China, in 2019, and then spread quickly in all around the world. This disease caused unprecedented deaths worldwide, with about 5 million deaths out of 265 million cases by December 5, 2021, according to the World Health Organization [12].

Among the important pathophysiological highlights of COVID-19, activation of inflammatory cascade can be mentioned. Accordingly, these could cause dysfunction in various organs including the brain with some symptoms such as olfactory and taste disorders, headache, dizziness, myalgia, delirium, confusion, irritability, the altered consciousness, depression, anxiety, stress, and insomnia. In addition, a number of severe neurological disorders such as encephalitis have been also observed in patients with COVID-19 disease [14, 15, 16, 79]. In this regard, clinical studies have shown that some patients infected with COVID-19 have symptoms similar to those of intracranial infections such as headache, epilepsy, and impaired consciousness [17, 18, 19, 20, 21].

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The interaction between the nervous system and the immune system is very complex, and depending on the context, it may cause a beneficial or detrimental effect on each other's performance. Among neurotransmitters, serotonin plays important roles in the immune system by central and peripheral mechanisms. Of note, delirium, confusion, and sleep disorders are associated with changes in the amounts of 5-HT and melatonin (as a 5-HT product). In addition, it has been shown that viral infections with subsequent cytokine storms may inhibit access to 5-HT and melatonin [16].

In this article, the effects of serotonergic system on the immune system by focusing on COVID-19 disease were reviewed.

## 2. Search methodology

This is a narrative review with PubMed and Google Scholar search using the keywords COVID-19, SARS-CoV-2, treatment of coronavirus, serotonin, and following terms: neuroimmunomodulation; neurotransmitter, cytokine storm, and immune response. A manual search of the references was additionally carried out.

## 3. SARS-CoV-2

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that is also commonly referred as COVID-19 is a member of the Coronaviridae family which attacks the epithelial cells of the respiratory tract, gastrointestinal tract, and vascular endothelial cells, as well as cells of various organs such as the kidneys, heart, and the brain [22, 23, 24]. The virus binds to angiotensin converting enzyme 2 (ACE2) receptors on the host cell membranes with the help of viral spike protein (S), a process that requires priming of protein S by proteolytic cleavages using host or virus-derived proteases [25, 26]. The stages of SARS-CoV-2 virus replication in the host cell can be divided into: (a) cell binding and internalization, (b) gene transcription and replication, (c) protein translation, and (d) assembly and release of virions [27].

Virus and/or virus-infected cells can stimulate the innate immune system, however when the immune response is hyperactive, it causes severe damage and in many cases leads to death [28, 29].

Coronavirus infection results in cytokine storm which is a life-threatening systemic inflammatory syndrome. Cytokine storm was shown to be associated with a significant increase in the concentrations of interleukins (ILs), especially IL-6, IL-2, IL-7, granulocyte colony-stimulating factor, interferon- $\gamma$ , monocyte chemoattractant protein 1, and TNF $\alpha$ , which may consequently cause lymphocyte apoptosis. Cytokine storm can be accompanied by the symptoms of COVID-19 such as fever, fatigue, anorexia, joint pain, nausea, vomiting, diarrhea, skin complications, rapid breathing, palpitations, hypotension, seizures, headache, hallucinations and tremors. Moreover, cytokine storm could also lead to tissue damage, thrombotic microangiopathy, and endothelial dysfunction [30, 31, 32, 33, 34, 35, 36, 38, 80].

Overall, it seems that the pathophysiology of COVID-19 involves a complex interaction of viral invasion and immune responses, but identifying the relative contribution of different pathways to the mortality of COVID-19 would not be easy. However, it will be interesting to discover compounds that may modulate these pathways through the various mechanisms that produce good clinical effects. Due to complex and multifaceted functions, serotonin can be an ideal candidate in controlling the development of COVID-19 complications.

## 4. Serotonin

### 4.1. Chemistry and physiological functions of serotonin

Serotonin is synthesized from the essential amino acid tryptophan in the diet, metabolized by monoamine oxidase to its major metabolite 5-hydroxy indole acetic acid (5-HIAA), and finally excreted in the urine [39]. Serotonin is a neurotransmitter involved in some physiological

functions such as mood, sleep, appetite, vomiting, pain perception, body temperature regulation, depression, anxiety, and migraines. Serotonin plays roles in the cardiovascular system, gastrointestinal tract (GI), respiratory tract, nervous system, and platelets [40].

### 4.2. Serotonin: immunomodulation

Serotonin is present in immune cells and its receptors are expressed at the membrane of immune cells [41]. Even exogenous 5-HT was found to induce the production of chemotactic factors by immune cells [42].

Numerous studies have previously indicated that 5-HT and its receptors, especially 5HT<sub>3</sub> receptors, are involved in the pathogenesis of chronic inflammatory conditions [43]. Therapeutic applications of 5HT<sub>3</sub> receptor antagonists have been reported in rheumatic diseases such as rheumatoid arthritis, as well as their anti-inflammatory properties and modulation of immune function, which lead to obtain some promising prospects regarding the treatment of incurable inflammatory diseases [44, 45].

It has also been shown that by increasing the severity of inflammation in rheumatoid arthritis, the concentration of 5-HT raises in the CNS [46].

Serotonin exerts its physiological functions in one of the following three ways: receptors, 5-HT transporter, and by covalent binding to various effector proteins. Almost all immune cells express at least one component of the serotonergic system, and some of body's immunomodulatory functions are related to 5-HT. For example, 5-HT in monocytes / macrophages modulates the immune mediators and cytokines' secretion such as TNF- $\alpha$ , interferon - $\gamma$ , IL-1 $\beta$ , IL-6, IL-8 and their related signaling pathways. In addition, the stimulation of neutrophils and T-cells by 5-HT can occur. The non-receptor mechanisms of the serotonergic system include 5-HT transporter, tryptophan hydroxylase-1, and nuclear factor- $\kappa$ B (NF- $\kappa$ B) [42, 47].

Various mechanisms may be responsible for the anti-inflammatory effects of 5HT<sub>3</sub> receptor antagonists. The stimulation of sensory neuron terminals by pain stimuli such as 5-HT leads to the release of neuropeptides such as substance P (SP) and calcitonin gene related peptide (CGRP). These peptides, besides causing pain, are powerful mediators of the inflammatory process and could stimulate immune cells to cause secondary release of other inflammatory mediators (including cytokines, prostaglandins, and leukotrienes). The inhibition of the 5HT<sub>3</sub> receptor blocks the stimulation of these cells by neuropeptides as well as inhibiting the release of inflammatory mediators such as TNF $\alpha$ , IL-2 $\beta$ , IL-6, and PGE<sub>2</sub> [48]. In addition to the inhibition of the release of neuropeptides, 5HT<sub>3</sub> antagonists could also inhibit the unmasking of tachykinin receptors [44].

The exact mechanism of 5HT<sub>3</sub> receptors in inflammation is unclear yet. At the same time, an interesting hypothesis has been proposed in this regard. During the inflammation induction, phosphorylation of 5HT<sub>3</sub> receptors occurs, which in turn involves some certain signaling pathways in order to release inflammatory mediators from immune cells. Binding the antagonist to the 5HT<sub>3</sub> receptor inhibits phosphorylation induced by inflammation and the subsequent functions [49].

In addition to the analgesic and anti-inflammatory effects of 5HT<sub>3</sub> receptor antagonists, the immunosuppressive effects of these drugs have been discussed as well. The inhibition of 5HT<sub>3</sub> receptors on lymphocytes has been demonstrated not only to inhibit lymphocyte proliferation, but also to inhibit gene expression and IL-2 production, which compete with cyclosporine. It also seems that these drugs, due to their immunosuppressive effect, will be suitable for autoimmune diseases as well as in organ transplantation [48].

### 4.3. Serotonin bell-shaped dose response curve

The bell-shaped dose-response curve of 5-HT and its antagonists has been reported [44, 81, 82]. In our previous study, granisetron increased the concentration of PGE<sub>2</sub> at low doses as well as decreasing it at higher

doses. On the contrary, the production of TNF $\alpha$  decreased with a low dose of granisetron and increased with higher doses [45].

The main mechanism of this effect is not clear yet. In the case of agonists, rapid desensitization of the receptors may be involved in this behavior. However, several factors may play role in antagonists' activity under such condition. For instance, higher doses of the drug may create a space barrier at the junction of the drug to the receptor. On the other hand, using different doses of antagonists may cause binding to different 5HT $_3$  receptor subtypes, including 5HT $_{3A}$  or 5HT $_{3AB}$ . In other words, if a difference exists in the density of receptors and their subtypes in different parts of the body, low doses and higher doses of drugs may cause different activities based on the type and receptor dispersion in each part. On the other hand, the hypothesis stating the low affinity binding to other receptors and creating additional effects with high doses can also be proposed. Blocking 5HT $_3$  receptors by antagonists appears to increase the access of other serotonergic receptors to 5-HT. Moreover, inflammatory or anti-inflammatory behavior of 5-HT are observed due to the activities of different subtypes of 5-HT receptors [44].

The complex nature of 5-HT, the presence of seven 5-HT receptors with 15 different subtypes (5 subtypes for 5HT $_3$  receptor) [42, 44] and the expression of 5-HT receptor genes during the inflammatory process that is time-dependent [52], complicates the analysis of the role of 5-HT antagonists in the immune system.

#### 4.4. Serotonin and its role in the symptoms of COVID-19

Carboxypeptidase A3 and 5-HT's blood concentrations, both of which are known as markers of mast cell stimulation, have been observed to increase and decrease in patients with COVID-19, respectively. Notably, serum carboxypeptidase A3 is a good marker for severe disease and 5-HT is a useful predictor of SARS-CoV-2 infection [53].

Although the symptoms of COVID-19 vary from patient to patient, some common clinical symptoms include fever, tiredness, cough, sore throat, anorexia, shortness of breath, headache, dizziness, bleeding from the lungs, nausea, vomiting, diarrhea, digestive discomfort, and lack of senses of smell and taste [54, 55].

Recent systematic reviews and meta-analyses have shown that the most common GI symptoms reported among COVID-19 patients include anorexia (15.8–26.8%), diarrhea (7.7–12.5%), nausea and vomiting (6–10.2%), and abdominal pain (3–9.2%). It is worth noting that these prevalence rates were reported in observational studies, which mainly include hospitalized COVID-19 patients and did not include all infected patients [56, 57].

The exact pathophysiological mechanism of GI symptoms in COVID-19 is still unknown. However, the evidence points out the roles of ACE $_2$  receptors and the inflammatory process induced by their stimulation in the GI tract. The respiratory system is one of the main places where the virus enters. Interestingly, ACE $_2$  receptors are highly expressed in the GI tract, making it another possible route for the transmission of SARS-CoV-2 infection [58].

In the gut, ACE $_2$  has a completely different function, which is independent of the renin-angiotensin system. ACE $_2$  stabilizes amino acid carriers such as B0AT1, and decreased ACE $_2$  function due to the occupation by the SARS-CoV-2 virus, may inhibit the intestinal absorption of some dietary amino acids for example tryptophan. This amino acid plays an important role in the body's immunity. In addition, 5-HT has a monoamine structure and its synthesis begins with tryptophan, which is converted to 5-hydroxytryptophan via the rate-limiting enzyme tryptophan hydroxylase. Thereafter, 5-hydroxytryptophan is rapidly decarboxylated by L-amino acid decarboxylase and then converted to 5-HT. Some evidences suggest that 5-HT concentrations are closely associated with irritable bowel syndrome (IBS). Besides, plasma 5-HT levels has been observed to increase in IBS with diarrhea. Therefore, targeting 5-HT signaling has been suggested as a useful way for reducing GI motility. Plasma 5-HT levels also increase with COVID-19, which is directly related to the severity of disease symptoms in these patients. Therefore,

lowering 5-HT levels may be an effective treatment strategy for patients with COVID-19 diarrhea [58, 59].

Ninety-five percent of the total amount of 5-HT is produced from enterochromaffin cells, and its presence locally is the main modulator of peristaltic movements in the GI tract. Some researchers have previously found that the breakdown of 5-HT to 5-HIAA metabolite slowly occurs in some COVID-19 patients with severe diarrhea. Afterward, 5-HT stays longer and then leads to diarrhea. On the other hand, an increase in 5-HT levels in diarrhea was indicated to be positively associated with an increase in IL-6, which is effective on exacerbating COVID-19 symptoms. Altogether, these data suggest that the elevated 5-HT may be associated with diarrhea and the severity of COVID-19 disease [60, 61].

After entering SARS-CoV-2 virus, the mediators released from the intestinal epithelium modulate the vagal afferent nerves. The results of this modulation process are as follows: sending a message to the brainstem; stimulating the area postrema; and causing nausea, vomiting and anorexia. Following the stimulation of ACE $_2$  receptors by the coronavirus, the mediators released from the GI epithelium result in exocytosis, inflammation, and apoptosis, and ultimately cause nausea and vomiting. Moreover, the concentration of angiotensin 2, which is the central stimulus of vomiting, increases due to receptor occupation. Entering the virus into the dorsal brainstem is also likely to provoke vomiting with late symptoms [57].

As it was reported, GI symptoms such as diarrhea and vomiting in patients with COVID-19 had a significant increase (49.5%) during patients' hospitalization, which may have been exacerbated by various drugs, including antibiotics. However, the importance of GI symptoms in the prognosis of patients with COVID-19 should not be underestimated [83].

The 5HT $_3$  receptor is present in immune cells, enterochromaffin cells, and peripheral and central neurons. As well, their antagonists are used to control nausea and vomiting after cancer chemotherapy, to control postoperative vomiting and diarrhea due to IBS, and to manage nausea and vomiting in patients with COVID-19 [57,63].

A group of researchers has previously claimed that the body's tryptophan is depleted among COVID-19 patients due to the decreased ACE $_2$ , which plays a key role in tryptophan absorption from food. In this regard, tryptophan is a precursor to the synthesis of 5-HT and its depletion consequently leads to a defect in the production of 5-HT, which is known as an important neuromodulator in olfactory neurons and taste buds, so that smell and taste senses may be lost in most COVID-19 patients [64].

In addition to dopamine, dopadocarboxylase (DDC) catalyzes the conversion of aromatic amino acids to their corresponding amines such as 5-hydroxytryptophan to 5-HT as well as L-histidine to histamine [65]. Recently, some changes in dopamine and 5-HT synthesis pathways have been implicated in the pathophysiology of COVID-19 virus. Since the gene expression, regulation of the function, and activity of ACE $_2$  and DDC enzymes occur similarly and in parallel, it seems that the possible roles of 5-HT, dopamine, and histamine also are similar in COVID-19. Defects in gene expression of ACE $_2$  due to SARS-CoV-2 consequently causes dysfunction of DDC and changes the concentration of these neurotransmitters among COVID-19 patients [16].

The current evidences suggest that advanced COVID-19 disease exacerbates the symptoms of Parkinson's disease and increases the need for dopamine in the affected patients. On the other hand, the loss of senses of smell and taste in some people infected with COVID-19 due to the ability of the coronavirus to enter the brain through the nasal canal is similar to that of Parkinson's disease, because the same symptoms were observed in patients with Parkinson's disease. The association between COVID-19 and Parkinson's disease may be due to the fact that the expression of the ACE $_2$  receptor gene located in dopamine neurons reduces in Parkinson's disease related to degenerative process of dopamine nerves. On the other hand, regarding the possible role of dopamine synthesis pathway in COVID-19 pathophysiology due to the dysfunction of DDC (which occurs in parallel and in coordination with ACE $_2$ ), it may cause both dopamine depletion and the need for drug use [66].

Angiogenesis has been reported to exist in the lungs of patients died due to COVID-19, which is approximately three times higher than that of influenza A (H1N1). In addition, the expressions of CXCL12/CXCR4 and consequently a high infiltration of T cells in the lungs of these patients severely increased. Accordingly, these findings are also consistent with inflammatory angiogenesis in some diseases such as colitis and malignant tumors [67]. Serotonin reuptake inhibitors, besides stimulating cell proliferation and antidepressant activity, could time-dependently induce the VEGF protein, which consequently promotes vascular permeability, endothelial cell proliferation, and angiogenesis. On the other hand, it is noteworthy that 5-HT itself stimulates endothelial cell proliferation by binding to 5HT<sub>2</sub> receptors [68]. Serotonin has the ability to stimulate angiogenesis and inflammation by inducing VEGF expression as well as stimulating endothelial proliferation. It was shown that granisterone-a 5HT<sub>3</sub> receptor antagonist-by reducing the effect of 5-HT or inhibiting the release of 5-HT from the nerve endings at the site of inflammation and the immune cells [48], decreases VEGF gene expression and endothelial cell proliferation, thereby inhibiting angiogenesis [45]. It can be speculated that drugs affecting the serotonergic system may play a role in the treatment of Covid-19 via modulating angiogenesis.

#### 4.5. Serotonin and gender in COVID-19 disease

In an *in vitro* animal study that was performed earlier, it was found that not only the severity of peripheral inflammation and angiogenesis were gender-dependent [69], but also 5-HT antagonist had some sex-modifying modulatory effects on peripheral inflammation and angiogenesis [84].

In this regard, a number of clinical reports have indicated that in COVID-19 patients, male patients had higher mortality, hospitalization, ICU admission, and intubation rates compared to female patients. The interactions among biological, hormonal, and gender factors may be responsible for the observed outcomes in men infected with COVID-19 [85].

Other studies have shown that women are less susceptible to viral infections and cytokine production. Female patients have high macrophage and neutrophil activities as well as higher rates of antibody production and response. In addition, ACE<sub>2</sub> is more expressed in some male tissues than in female ones, which may explain the differences observed in susceptibility and severity of COVID-19 disease between male and female patients [72].

Considering all the evidences as well as conducting further studies in this field in the future, interesting approaches to the treatment of COVID-19 may be achieved by interfering with the serotonergic system.

#### 5. COVID-19 treatment approach and the role of serotonergic system

The rapid spread of SARS-CoV-2 infection and the lack of definitive treatment have led researchers to think more about using previously proposed drugs with a new approach. The use of selective 5-HT reuptake inhibitors (SSRIs) can be considered as an adjunctive therapy in COVID-19. These medications were introduced to the world's pharmaceutical market more than three decades ago, and their pharmacological properties are well-known, so they may be considered as potential safe treatments for COVID-19.

Previous clinical and experimental studies supported the hypothesis that 5-HT can help to reduce cytokine overproduction under severe and systemic inflammatory conditions caused by COVID-19 and to reduce its harmful consequences. Serotonin not only can act directly by binding to its receptors in immune cells, but it can also act via the central nervous system for instance the process of the vagal anti-inflammatory reflex [73].

Fluoxetine (a SSRI) shows some anti-inflammatory and anti-viral properties in COVID-19 by modulating the immune system; therefore,

it may be useful as an adjunct therapy under this condition. It may also reduce the levels of proinflammatory chemokines/cytokines (such as CCL-2, IL-6, and TNF- $\alpha$ ) among COVID-19 patients. In addition, fluoxetine may be able to reduce the neurological complications caused by COVID-19 [74].

In addition, some evidences have shown that SSRIs such as fluvoxamine and sertraline could be effective as adjunctive therapy in SARS-CoV-2. The direct action on the immune system along with other indirect mechanisms of drugs affecting the serotonergic system can be used to regulate the enhanced immune response and to reduce the symptoms of the disease. Moreover, it is important to note that patients on long-term use of SSRIs should continue their medications during their hospitalization due to COVID-19 [75,76].

Plasma 5-HT may be responsible for many clinical pulmonary and extra pulmonary manifestations of severe type of COVID-19 disease. There is an evidence that 5HT<sub>2</sub> antagonist by reducing pulmonary platelet entrapment, inhibiting platelet activation and aggregation, facilitating respiration, reducing the risk of pulmonary fibrosis, and dealing with the severe adverse consequences of COVID-19 on the kidneys, nervous system, and cardiovascular system, may reverse 5-HT-mediated pulmonary vasoconstriction. In this regard, cyproheptadine as a safe, inexpensive, and available oral 5HT<sub>2</sub> antagonist that could be considered as a treatment option for COVID-19, should be further investigated [77].

In addition, ketanserin - 5HT<sub>2 $\alpha$</sub>  receptor antagonist-could inhibit 5-HT-induced vasoconstriction and improve perfusion of affected parts of the lungs in COVID-19 patients. Moreover, ketanserin could inhibit 5HT<sub>2 $\alpha$</sub>  mediated platelet aggregation and prevent thrombosis, which consequently result in a reduction in 5-HT release. Considering the combined effect of ketanserin on pulmonary vasoconstriction and platelet aggregation, it seems that further evaluations of its therapeutic effect in COVID-19 patients are needed [78].

In regard to numerous reports on the bell-shaped dose-response curve of 5-HT and its antagonists [44, 45, 81, 82] in all its new indications, determining the dose of these drugs is known as a key and important parameter, especially in the case of COVID-19.

#### 6. Conclusion

In summary, it was indicated that 5-HT by modulating the immune system along with other indirect mechanisms, can effectively reduce the intensified immune response and prevent the consequent neurological and other complications. Although scientific evidence suggests the use of drugs affecting the serotonergic system as an adjunct intervention in SARS-CoV-2 infection, the exact effects of this system on patients with COVID-19 is not fully understood yet. Future experimental and clinical studies are needed to understand the exact role of serotonergic system in COVID-19 disease.

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### Additional information

No additional information is available for this paper.

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