Brief Communication

Determining the relationship between SARS-CoV-2 infection, dopamine, and COVID-19 complications

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Abstract

**Objectives:** There is compelling evidence that aged, immunosuppressed, and chronically ill patients are a high-risk group for increased mortality upon infection with the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This study investigated the contribution of morbidities and related prescribed medications to COVID-19 associated mortality.

**Methods:** Based on the various recently reported clinical scenarios a theoretical framework was designed to shed light on the mode of infection of the central nervous system by SARS-CoV-2 and possible management options.

**Results:** Dopamine-release mechanisms in the central nervous system may play a major role in the entry and propagation of coronaviruses.

**Conclusion:** This study emphasizes the need for a thorough and urgent investigation of the dopamine-release pathways in the central nervous system. These efforts will help find a definitive cure for the pandemic coronavirus disease (COVID-19).

Keywords: Central nervous system infection; COVID-19; Dopamine; SARS-CoV-2

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Introduction

The new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an interesting virus that, without doubt, has changed the entire globe. Governments and organisations all over the world are trying to fight it by every possible means, yet no definitive treatment was reported. Several studies are currently addressing the potential neurological impact of SARS-CoV-2 upon clinical reports of neural manifestations associated with the coronavirus disease 2019 (COVID-19). Of note, patients with severe COVID-19 can also experience cytokine storm syndrome, which is an important sign of breakdown of the blood—brain-barrier. These neurological manifestations are considered rare in usual viral infections. Nevertheless, the link between coronavirus invasion and neural manifestations remains unclear.\(^1\)–\(^3\)

This study aimed to identify alternative binding mechanisms of SARS-CoV-2 in the human body. Besides the common angiotensin-converting enzyme 2 (ACE2) receptor, other cellular receptors should be investigated as new coronaviruses may exploit other alternative pathways. The first suspected receptor or co-receptor is dopamine. To date, no investigation has explored the potential role of dopamine and dopaminergic receptors on SARS-CoV-2 infection and COVID-19. Nevertheless, dopamine may downregulate the...
immune response during infection, thereby enhancing the life cycle of SARS-CoV-2, which may be particularly relevant in patients receiving medications containing dopamine agonists. The mortality rate among the aged population with COVID-19 increases when systemic conditions are present, such as diabetes and dementia, or in immunosuppressed patients, who usually use dopamine-agonist-containing medicines. Hence, SARS-CoV-2 may exploit dopamine as an entry pathway in the body, with dopamine receptors supporting the virus pathogenicity.

**Dopamine and viruses**

It is known that dopaminergic receptors are involved in the entry of various virus. For example, elevated dopamine can significantly enhance the onset of the human immunodeficiency virus (HIV) and related central nervous system (CNS) infections by up-regulating the expression of HIV entry co-receptors and enabling the virus to evade macrophages during early infection stages. Surprisingly, dopamine-antagonists can inhibit this mechanism. The Japanese encephalitis virus (JEV) can disrupt the blood—brain-barrier and cause viral encephalitis. JEV exploits dopamine signalling to facilitate the infectious process by significantly increasing dopamine levels, this increase might be implicated in the susceptibility of neighbouring cells to JEV through the stimulation of dopamine receptor D2 (D2DR).

Based on these findings, SARS-CoV-2 may mimic the behavioural CNS pathogenic mechanism of JEV and HIV during the early stages of COVID-19.

**Assumptions**

1 SARS-CoV-2 may exploit dopaminergic receptors to improve its life-cycle, increasing viral entry chances.
2 Dopamine-agonist drugs may disrupt the respiratory system by affecting the carotid body chemosensitivity, resulting in decreased oxygen levels and worsen ventilation response.
3 SARS-CoV-2 hinders the innate and adaptive immune responses via dopamine-mediated disruption of intracellular biosynthesis (see Figure 1).

Several clinical observations support this hypothesis. First, the neurological manifestations often appear after the diagnosis of the COVID-19, similar to some neurotropic microbial infections. Dopaminergic receptors can enhance the chance of binding of some viruses to the CNS to initiate viral encephalitis in the early stages of viral infection. An example of this mechanism is D2DR in cases of HIV and JEV encephalopathy. Moreover, the viral life-cycle of SARS-CoV-2 may be enhanced in the presence of high levels of catecholamine, possibly by binding to dopaminergic receptors and increasing the chance of viral entry.

**Figure 1:** A. Entry phase of the virus: it is possible that after the initial binding of SARS-CoV-2 to ACE2 receptors, the Spike-like protein of the virus binds to dopaminergic receptors of neighbouring cells. The presence of dopamine receptors in the brain plays an integral regulatory role in local immunity (e.g. lymphocytes, cytokines). Cytokines or neurokines have a regulatory function in both nervous and the immune systems. In addition, dopamine at certain concentrations can inhibit the lymphocytic function. B. The influx of dopamine causes further decrease in both the innate and adaptive immunity that helps increasing the viral load. This leads to more neural manifestations, such as encephalopathy, fatigue, dizziness, unconsciousness, among others. Increased production of D1-like receptors (D1) results in increased expression of cAMP, which causes a decrease in the innate immune response; whereas high expression of D2-Like receptors (D2) results in a cytokine storm that leads to a reduction of the adaptive immune response.
Second, increased dopamine reduces oxygen levels, especially when considering the “Happy Hypoxaemia” associated with COVID-19.\(^1\)\(^,\)\(^2\) This happens as dopamine has a known ability to blunt the ventilatory response of the human basal carotid body to hypoxia.\(^3\)\(^,\)\(^4\) Therefore, SARS-CoV-2 and dopamine could share the responsibility for impaired ventilation. Some drugs (e.g. haloperidol) block the response to exogenous dopamine, but do not alter ventilation response during normoxia or hypoxia, suggesting that either the endogenous dopamine does not play a role in determining the steady-state chemoreceptor discharge or the endogenously released dopamine may have access to receptors that are relatively inaccessible to exogenous blockers.\(^5\)\(^,\)\(^6\)

Third, dopamine is a regulator of immune function. The virus may manipulate the immune system by increasing the levels of dopamine to increase the possibility of viral entry. Increased D1-like receptor agonists, such as dopamine, can stimulate cAMP production,\(^7\) which generally suppresses innate immune functions.\(^8\) On the other hand, increasing D2-like receptors results in the inhibition of the adaptive immune response.\(^9\) A possible explanation is the exacerbation of pro-inflammatory responses that will worsen the pathogenic condition.\(^10\) Here, the exhaustion of T-cells could have led to the progression of the COVID-19. Therefore, in both innate and adaptive responses, the presence of SARS-CoV-2 infection will result in high interleukin (IL)-6 levels.\(^11\) In keratinocytes, “dopamine stimulated the production of IL-6 and IL-8 in a concentration-dependent manner”.\(^12\) Thus, these findings suggest that dopamine plays a primary role in reducing the host immunity and increasing the chance for severe complications.

Lastly, a recent study discussed different drugs interacting with SARS-CoV-2. We found that the top three medications among the 10 tested drugs had a direct influence on dopamine secretion. One of these drugs was identified in a very recent Chinese study as having the most beneficial outcome. Among the 10 tested drugs had a direct influence on dopamine secretion. One of these drugs was identified in a very recent Chinese study as having the most beneficial outcome.

In conclusion, a review of the composition of drugs used in the treatment of Covid-19.

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Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

The current study does not involve any living being to declare any ethical issues. It is a theoretical framework for the treatment of Covid-19.

Authors contributions

KMM and KAM conceptualized and designed the study; provided research materials; hypothesised, collected, analysed, and interpreted data; wrote the manuscript, and critically reviewed the final draft. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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