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Selective Neuronal Mitochondrial Targeting in SARS-CoV-2 Infection Affects Cognitive Processes to Induce 'Brain Fog' and Results in Behavioral Changes that Favor Viral Survival

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Alterations in brain functioning, especially in regions associated with cognition, can result from infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and are predicted to result in various psychiatric diseases. Recent studies have shown that SARS-CoV-2 infection and coronavirus disease 2019 (COVID-19) can directly or indirectly affect the central nervous system (CNS). Therefore, diseases associated with sequelae of COVID-19, or 'long COVID', also include serious long-term mental and cognitive changes, including the condition recently termed 'brain fog'. Hypoxia in the microenvironment of select brain areas may benefit the reproductive capacity of the virus. It is possible that in areas of cerebral hypoxia, neuronal cell energy metabolism may become compromised after integration of the viral genome, resulting in mitochondrial dysfunction. Because of their need for constant high metabolism, cerebral tissues require an immediate and constant supply of oxygen. In hypoxic conditions, neurons with the highest oxygen demand become dysfunctional. The resulting cognitive impairment benefits viral spread, as infected individuals exhibit behaviors that reduce protection against infection. The effects of compromised mitochondrial function may also be an evolutionary advantage for SARS-CoV-2 in terms of host interaction. A high viral load in patients with COVID-19 that involves the CNS results in the compromise of neurons with high-level energy metabolism. Therefore, we propose that selective neuronal mitochondrial targeting in SARS-CoV-2 infection affects cognitive processes to induce 'brain fog' and results in behavioral changes that favor viral propagation. Cognitive changes associated with COVID-19 will have increasing significance for patient diagnosis, prognosis, and long-term care.

MeSH Keywords: Coronavirus • COVID-19 • Hypoxia, Brain • Mitochondria

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Cerebral infection with SARS-CoV-2 results in acute and chronic pathologic changes [1–3]. Because this new pandemic infection has been studied clinically for less than a year, the long-term effects on the CNS, including whether SARS-CoV-2 causes or accelerates the clinical course of neurodegenerative diseases, such as Parkinson disease and Alzheimer disease, remain unknown [1]. Interestingly, there have now been several studies that have shown that infection with SARS-CoV-2 affects cognitive function and is associated with mental illness, including depression, and developmental or functional CNS changes, including autism [4–13]. Recently, patients with COVID-19 and CNS involvement have shown psychological symptoms, behavioral changes, cognitive impairment, confusion, and poor concentration; collectively termed 'brain fog' [14].

It is now known that the initial pulmonary infection with SARS-CoV-2 damages the alveoli and impairs alveolar oxygenation. COVID-19 pneumonia can result in acute respiratory distress syndrome, hypoxemia, and acidosis [15–17]. The degree of initial lung damage can determine the long-term effects of infection and may be associated with acute and chronic changes in the heart and CNS [15–17]. Recent modeling data have shown that the genomic and subgenomic RNA (sgRNA) transcripts of SARS-CoV-2 can take over the host cell by involving the mitochondrial matrix and nucleolus [18]. It is possible that SARS-CoV-2 can directly impair mitochondrial energy metabolism via targeted action on oxygen availability and utilization [18–20]. Importantly, these effects may result from the integration of the viral genome into the host cell mitochondrial matrix, resulting in a viral-mitochondrial interaction or viral 'hijacking' of the mitochondrial genome [18–20]. This viral-mitochondrial interaction depends on enhanced energy and reduced host immune responsiveness, promoting viral replication and survival [19–21]. Therefore, these pathological effects of SARS-CoV-2 infection may explain the long-term psychiatric, cognitive, and neurodegenerative sequelae of CNS infection (**Figure 1**) [13]. Also, the generation of an effective host immune response will be impaired when the available mitochondrial energy is reduced [13].

The role of impaired mitochondrial function and energy metabolism in SARS-CoV-2 infection may also explain the development of impaired cognitive function in CNS infection. Mitochondria evolved from bacteria, and retain the ability to move between cells and toward hypoxic microenvironments, as well as to exist in extracellular environments such as cerebrospinal fluid [21–24]. We previously speculated that mitochondria represent the initial step in the cellular stress response [25]. Their unique oxygen-sensitive functions highlight the significance of mitochondria in initiating pro-inflammatory reactions [25].

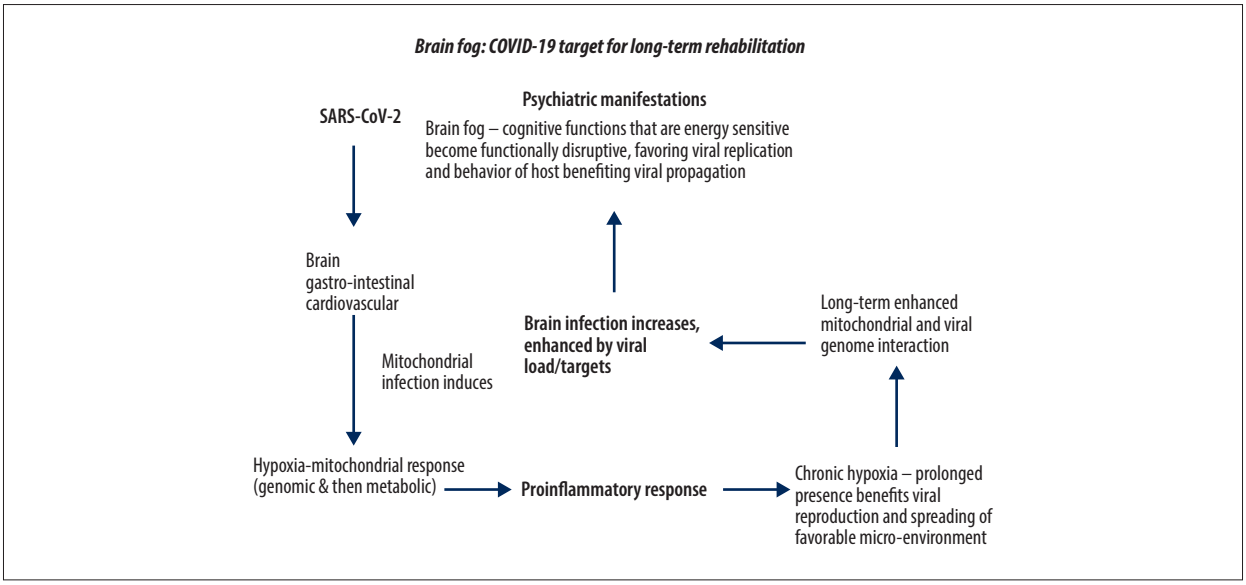

Figure 1. 'Brain fog' and COVID-19 targeting for long-term rehabilitation. SARS-CoV-2, which causes COVID-19, can infect the lungs, CNS, gastrointestinal system, and cardiovascular system. With time, widespread infection increases the total viral load in the infected individual. SARS-CoV-2 can integrate its genome into mitochondria to reduce energy metabolism. The brain is especially vulnerable to hypoxia because cognitive neural processes adjust poorly to hypoxic conditions. Hypoxia is also pro-inflammatory. Therefore, as the viral load increases, cognitive impairment and confusion increase, a condition known as 'brain fog'. This ongoing cascade of neuronal dysfunction is an important factor in understanding the long-term pathogenesis of CNS infection with SARS-CoV-2. Importantly, the behaviors resulting from 'brain fog' may increase the spread of SARS-CoV-2. COVID-19 – coronavirus disease 2019; SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2; CNS – central nervous system.

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It has previously been reported that several neurological disorders can be initiated by chronic inflammation [26,27]. Physiological stress caused by inflammation can increase susceptibility to viral infection [26,27]. Given the dependence of neural tissue on high oxygen levels, the effects of mitochondrial dysfunction associated with SARS-CoV-2 infection may underlie the observed COVID-19-associated neurological effects [26,27]. Targeted involvement of the mitochondria in SARS-CoV-2 may also involve mitochondrial synchronization in multiple cells [27–29]. Combined with its induced pro-inflammatory response, SARS-CoV-2 infection leads to neuronal dysfunction, resulting in 'brain fog', as cognition requires a high and uninterrupted supply of oxygen (**Figure 1**) [3]. If energy metabolism is compromised, the resulting impairment of the immune response serves to increase the spread of the virus within an individual and between individuals. Therefore, the development of 'brain fog' as a long-term outcome of SARS-CoV-2 infection may be considered to be an evolutionarily conserved and strategic mechanism on the part of the virus that aids its spread and survival.

Conclusions

Recent studies and clinical observations of SARS-CoV-2 infections have yielded insights into the cellular and physiological processes that enhance the ability of the virus to reproduce and spread, including its need for a highly oxygenated microenvironment [28]. Recently, there has been an increased understanding of the possible role of compromised mitochondria in the pathogenesis of SARS-CoV-2 infection. Mitochondrial energy metabolism responds immediately to a hypoxic microenvironment, and mitochondria can serve as mobile sentinel organelles that can act together as an energy delivery system [25]. Given the high energy and oxygenation requirements in neural tissue, mitochondria can serve as indicators of early acute neuronal dysfunction. The relationship between cognitive function, mental health, virus susceptibility, and viral infectivity may be a function of CNS viral load, which increases with time in the case of 'long-term COVID'. The resulting cognitive impairment benefits viral spread, as infected individuals exhibit reduced anti-infection behaviors (**Figure 1**). The effects of compromised mitochondrial function may also be an evolutionary advantage for SARS-CoV-2 in terms of its interaction with the host. A high viral load in COVID-19 patients that involves the CNS results in the compromise of neurons with high levels of energy metabolism. Therefore, we propose that selective neuronal mitochondrial targeting in SARS-CoV-2 infection affects cognitive processes to induce 'brain fog' and results in behavioral changes that favor viral survival and propagation. Cognitive changes associated with COVID-19 will have increasing significance in patient diagnosis, prognosis, and long-term care. Therefore, there will be an increasing need for support for mental health issues related to COVID-19. Long-term therapeutic strategies for COVID-19 should combine pharmacological agents targeting a chronic ischemic neural pro-inflammatory environment with behavioral activities to restore cognitive function [29,30].

Conflict of interest

None.

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