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Viral Targeting of Mitochondria May Alter Cognition and Enhance Viral Transmission

by George B. Stefano[1]

[1]Department of Psychiatry, First Faculty of Medicine, Charles University and General University Hospital in Prague, 120 00 Prague, Czech Republic

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While several recent studies highlighted the acute and chronic changes resulting from infection with severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) (Wang, Kream and Stefano, 2020; Chen et al., 2020; Pezzini and Padovani, 2020), the long-term effects of COVID-19 on the CNS remain largely unknown (Wang, Kream and Stefano, 2020). The results of several recent studies revealed that SARS-CoV-2 infection can lead to altered cognitive function and neuropsychiatric and developmental disorders, including depression and autism, respectively (Lau et al., 2004; Tsai et al., 2004; Correa-Palacio et al., 2020; Chandra et al., 2020; Mawhinney et al., 2020; Beach et al., 2020; Epstein et al., 2020; Chen et al., 2020; Zhang and Ma, 2020; Ptáček et al., 2020). The psychological symptoms, behavioral changes, cognitive impairment, confusion, and poor concentration resulting from SARS-CoV-2 infection are components of a characteristic "brain fog" (Croall et al., 2020).

The degree of initial lung damage resulting from an acute SARS-CoV-2 infection has an impact on the long-term effects of infection and may lead to both acute and chronic changes in the central nervous system (CNS) (Calabrese et al., 2020; Tian et al., 2020; Xu et al., 2020). Findings from recent modeling studies suggest that both genomic and subgenomic RNA SARS-CoV-2 transcripts can hijack the host cell by targeting the nucleolus and the mitochondrial matrix (Wu et al., 2020). Specifically, the SARS-CoV-2 pathogen may integrate components of its genome into the mitochondrial matrix of the host cell, thereby impairing mitochondrial energy metabolism by reducing the availability and utilization of oxygen (Wu et al., 2020; Shenoy, 2020; Singh et al., 2020). This viral-mitochondrial interaction results in enhanced energy use, a reduction in available mitochondrial energy, and reduced immune responses by the host cell, thereby promoting virus replication and survival (Shenoy, 2020; Singh et al., 2020; Stefano, Esch and Kream, 2020; Ptáček et al., 2020). These pathological effects may lead to some of the long-term cognitive, psychiatric, and neurodegenerative sequelae of this infection (Ptáček et al., 2020).

The mechanisms used by SARS-CoV-2 to alter host cell mitochondrial function and energy metabolism may lead to the development of impaired cognitive function. Cellular mitochondria evolved from an alphaproteobacterial-like bacterial ancestor and have retained the ability to move between cells and toward hypoxic microenvironments and to exist extracellularly, for example, in the cerebrospinal fluid (Stefano, Esch and Kream, 2020; Stefano, Esch and Kream, 2019; Hayakawa et al., 2018; Nakamura, Park and Hayakawa, 2020). In our previous studies, it was suggested that mitochondrial targeting may be an initial step in the cellular stress response to infection and similar perturbations given their unique oxygen-sensitive functions that are critical factors initiating protective

proinflammatory reactions (Esch et al., 2020).

Physiological stress resulting from inflammation can increase one's susceptibility to viral infection; furthermore, several neurological disorders have been linked to chronic inflammation. (Esch and Stefano, 2002; Esch et al., 2002). Certain viruses, for example, human immunodeficiency virus can enter the CNS by hijacking immune cells to facilitate penetration through the blood-brain barrier (BBB) (Stefano et al., 2021; Stefano et al., 2022). Thus, normal cell trafficking through the BBB can introduce pathogens into the CNS, which occurs at higher frequency in activated immune cells, further implying the susceptibility of the BBB and questioning its' barrier nature. These virus pathogens can utilize complementary conformational shape matching to target mitochondria and perturb pathways leading to energy production, thereby altering cognition, because of its constant need for high levels of energy to function (Stefano et al., 2021; Stefano et al., 2022). Of note, mitochondria may represent the ideal target for these viruses because of their bacterial origin; this permits the viruses to replicate their evolutionarily ancient interactions (Stefano and Kream, 2022; Stefano et al., 2022; Büttiker et al., 2023; Stefano et al., 2023). Overall, virus-mediated impairment of mitochondrial function and cognition may lead to alterations in both cognitive and noncognitive protective behaviors that lead to increased infectivity and transmission (Stefano et al., 2021).

SARS-CoV-2 infection may also lead to mitochondrial synchronization in multiple cells (Esch et al., 2002; Tobin, Laghi and Jubran, 2020; Huang et al., 2018). Furthermore, if energy metabolism is compromised, the resulting immune dysfunction will increase the spread of the virus both within and ultimately between individuals. Because neural tissue requires high oxygen levels to function optimally, mitochondrial dysfunction resulting from SARS-CoV-2 infection may lead to one or more COVID-19-associated neurological sequelae (Esch and Stefano, 2002; Esch et al., 2002). Therefore, the development of "brain fog" as an outcome of SARS-CoV-2 infection may be the result of a conserved strategic mechanism used by the virus pathogen to promote its transmission and long-term survival.

In summary, SARS-CoV-2 infection has been associated with altered brain function which may lead to new onset or worsening of preexisting neuropsychiatric symptoms. Recent studies have considered both the direct and indirect impact of SARS-CoV-2 infection on the CNS. Among these findings, prolonged COVID-19 (also known as "long COVID") may lead to serious long-term mental and cognitive changes, including the condition known as "brain fog". Neuronal cell energy metabolism may become compromised upon integration of the viral genome, resulting in mitochondrial dysfunction and distinct regions of cerebral hypoxia. As discussed, hypoxic conditions in the CNS may facilitate virus reproduction. Cerebral tissues require an immediate and constant supply of oxygen to maintain physiologic function. Thus, when confronted with hypoxic conditions, neurons with the highest oxygen demand become dysfunctional. The resulting cognitive impairment serves to benefit the viral pathogen, as infected individuals exhibit behaviors that limit protection against infection. The capacity to target cellular mitochondria may also provide an evolutionary advantage for SARS-CoV-2. A high viral load detected in COVID-19 patients with CNS-related symptoms suggests that neurons with high-level energy needs have been compromised. Therefore, it is proposed that the selective targeting of neuronal mitochondria during SARS-CoV-2 infection affects cognitive processes and results in "brain fog" and behavioral changes that favor viral propagation. Cognitive changes associated with COVID-19 are clearly of increasing significance with respect to patient diagnosis, prognosis, and the need for long-term care. Furthermore, this cloaked abeyant nature of certain pathogens and/or their metabolites may represent initiating neuropsychiatric and/or neurodegenerative phenomena that currently eludes detection. Taken together, there is an increasing need for mental health support for issues related to acute and chronic pathogen actions, e.g., COVID-19 (Huang et al., 2018; von Arnim et al., 2019).

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References

Beach, S. R., Praschan N., Hogan C., Dotson, S., Merideth, F., Kontos, N., Fricchione, G. L., & Smith, F. A. (2020). Delirium in COVID-19: a case series and exploration of potential mechanisms for central nervous system involvement." *General Hospital Psychiatry 65*, 47–53. https://doi.org/10.1016/j.genhosppsych.2020.05.008.

Büttiker, P., Weissenberger, S., Esch, T., Anders, M., Raboch, J., Ptáček, R., Kream, R. M., & Stefano, G. B. (2023). Dysfunctional mitochondrial processes contribute to energy perturbations in the brain and neuropsychiatric symptoms. *Frontiers in Pharmacology 13*. https://doi.org/10.3389/fphar.2022.1095923.

Calabrese, F., Pezzuto, F., Fortarezza, F., Hofman, P., Kern, I., Panizo, Á., Von Der Thüsen, J., Timofeev, S., Gorkiewicz, G., & Lunardi, F. (2020). Pulmonary pathology and COVID-19: lessons from autopsy. the experience of European pulmonary pathologists. *Virchows Archiv 477*(3), 359–372. https://doi.org/10.1007/s00428-020-02886-6.

Chandra, P. S., Shiva, L., Nagendrappa, S., Ganjekar, S., & Thippeswamy, H. (2020) COVID-19 related psychosis as an interface of fears, socio-cultural issues and vulnerability- case report of two women from India." *Psychiatry Research 290*, 113136. https://doi.org/10.1016/j.psychres.2020.113136.

Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., Qiu, Y., et al. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet 395*(10223), 507–513. https://doi.org/10.1016/s0140-6736(20)30211-7.

Chen, X., Laurent, S., Onur, O. A., Kleineberg, N. N., Fink, G. R., Schweitzer, F., & Warnke, C. (2020). A systematic review of neurological symptoms and complications of COVID-19. *Journal of Neurology 268*(2), 392–402. https://doi.org/10.1007/s00415-020-10067-3.

Correa-Palacio, A., Hernández-Huerta, D., Gómez-Arnau, J., Loeck, C. & Caballero, I. (2020). Affective psychosis after COVID-19 infection in a previously healthy patient: a case report. *Psychiatry Research* 290, 113115. https://doi.org/10.1016/j.psychres.2020.113115.

Croall, I. D., Hoggard, N., Aziz, I., Hadjivassiliou, M., & Sanders D. S. (2020). Brain fog and non-coeliac gluten sensitivity: proof of concept brain MRI pilot study. *PLOS ONE 15*(8), e0238283. https://doi.org/10.1371/journal.pone.0238283.

Epstein, D., Andrawis, W., Lipsky, Ziad, H. A., & Matan, M. (2020). Anxiety and suicidality in a hospitalized patient with COVID-19 infection. *European Journal of Case Reports in Internal Medicine*, *7*(5), 1. https://doi.org/10.12890/2020_001651.

Esch, T., Stefano, G. B., Fricchione, G. L., & Benson, H. (2002) The role of stress in neurodegenerative diseases and mental disorders. *Neuroendocrinology Letters*, *223*(3), 199–208.

Esch, T., Stefano, G. B., Ptáček, R., & Kream, R. M. (2020). Emerging roles of blood-borne intact and respiring mitochondria as bidirectional mediators of pro- and anti-inflammatory processes. *Medical Science Monitor 26*. https://doi.org/10.12659/msm.924337.

Esch, T., & Stefano, G. B. (2002) Proinflammation: a common denominator or initiator of different pathophysiological disease processes. *Medical Science Monitor 8*(5), HY1–HY9.

Hayakawa, K., Bruzzese, M., Chou, S., Ning, M., Ji, X., & Lo, E. H. (2018). Extracellular mitochondria for therapy and diagnosis in acute central nervous system injury. *JAMA Neurology 75*(1), 119. https://doi.org/10.1001/jamaneurol.2017.3475.

Huang, L., Ma, Q., Li, Y., Li, B., and Zhang, L. (2018). Inhibition of microRNA-210 suppresses pro-inflammatory response and reduces acute brain injury of ischemic stroke in mice." *Experimental Neurology 300*, 41–50. https://doi.org/10.1016/j.expneurol.2017.10.024.

Lau, K. K., Yu, W. C., Chu, C. M., Lau, S. T., Sheng, B., & Yuen, K.-Y. (2004). Possible central nervous system infection by SARS coronavirus. *Emerging Infectious Diseases 10*(2), 342–344. https://doi.org/10.3201/eid1002.030638.

Mawhinney, J. A., Wilcock, C., Haboubi, H., & Roshanzamir, S. (2020). Neurotropism of SARS-CoV-2: COVID-19 presenting with an acute manic episode." *Case Reports 13*(6). https://doi.org/10.1136/bcr-2020-236123.

Nakamura, Y., Park, J., & Hayakawa, K. (2020). Therapeutic use of extracellular mitochondria in CNS injury and disease." *Experimental Neurology* 324. https://doi.org/10.1016/j.expneurol.2019.113114.

Pezzini, A., & Padovani, A. (2020). Lifting the mask on neurological manifestations of COVID-19. *Nature Reviews Neurology 16*(11), 636–644. https://doi.org/10.1038/s41582-020-0398-3.

Ptáček, R., Ptáčková, H., Anders, M., & Stefano, G. B. (2020) Psychiatric manifestations of COVID-19 and their social significance. *Medical Science Monitor 26*. https://doi.org/10.12659/msm.930340.

Shenoy, S. (2020). Coronavirus (COVID-19) sepsis: revisiting mitochondrial dysfunction in pathogenesis, aging, inflammation, and mortality. *Inflammation Research 69*(11), 1077–1085. https://doi.org/10.1007/s00011-020-01389-z.

Singh, K. K., Chaubey, G., Chen, J. Y., & Suravajhala, P. (2020). Decoding SARS-CoV-2 hijacking of host mitochondria in COVID-19 pathogenesis. *American Journal of Physiology-Cell Physiology 319*(2), 258–267. https://doi.org/10.1152/ajpcell.00224.2020.

Stefano, G. B., Esch, T., & Kream, R. M. (2019). Behaviorally-mediated entrainment of whole-body metabolic processes: conservation and evolutionary development of mitochondrial respiratory complexes." *Medical Science Monitor 25*, 9306–9309. https://doi.org/10.12659/msm.920174.

Stefano, G. B., Esch, T., & Kream, R. M. (2020). potential immunoregulatory and antiviral/SARS-COV-2 activities of nitric oxide. *Medical Science Monitor 26*. https://doi.org/10.12659/msm.925679

Stefano, G. B., Büttiker, P., Weissenberger, S., Esch, T., Anders, M., Raboch, J., Kream, R. M., & Ptáček, R. (2023) Independent and sensory human mitochondrial functions reflecting symbiotic evolution." *Frontiers in Cellular and Infection Microbiology 13*. https://doi.org/10.3389/fcimb.2023.1130197.

Stefano, G. B., Büttiker, P., Weissenberger, S., Ptáček, R., Wang, F., Esch, T., Bilfinger, T. V., & Kream, R. M. (2022). Biomedical perspectives of acute and chronic neurological and neuropsychiatric sequelae of COVID-19." *Current Neuropharmacology 20*(6), 1229–1240. https://doi.org/10.2174/1570159x20666211223130228.

Stefano, G. B., & Kream, R. M. (2021). Mitochondrial DNA heteroplasmy as an informational reservoir dynamically linked to metabolic and immunological processes associated with COVID-19 neurological disorders." *Cellular and Molecular Neurobiology 42*(1), 99–107. https://doi.org/10.1007/s10571-021-01117-z.

Stefano, G. B., Ptáček, Ptáčková, H., Martin, A., & Kream, R. M. (2021). 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." *Medical Science Monitor 27*. https://doi.org/10.12659/msm.930886.

Stefano, G. B., Büttiker, P., & Kream, R. M. (2022). Reassessment of the blood-brain barrier: a potential target for viral entry into the immune-privileged brain." *Germs 12*(1), 99–101. https://doi.org/10.18683/germs.2022.1310.

Tian, S., Xiong, Y., Liu, H., Niu, L., Guo, J., Liao, M., & Xiao, S. Y. (2020). pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies. *Modern Pathology 33*(6), 1007–1014. https://doi.org/10.1038/s41379-020-0536-x.

Tobin, M. J., Laghi, F., & Jubran, A. (2020). Why COVID-19 silent hypoxemia is baffling to physicians. *American Journal of Respiratory and Critical Care Medicine 202*(3), 356–360. https://doi.org/10.1164/rccm.202006-2157cp.

Tsai, L.-K., Hsieh, S.-T., Chao, C.-C., Chen, Y.-C., Lin Y.-M., Chang, S.-C., & Chang, Y.-C. (2004). Neuromuscular disorders in severe acute respiratory syndrome. *Archives of Neurology 61*(11), 1669. https://doi.org/10.1001/archneur.61.11.1669.

von Arnim, C. A. F., Bartsch, T., Jacobs, A. H., Holbrook, J., Bergmann, P., Zieschang, T., Polidori, M. C., & Dodel, R. (2019). Diagnosis and treatment of cognitive impairment. *Zeitschrift Für Gerontologie Und Geriatrie 52*(4), 309–315. https://doi.org/10.1007/s00391-019-01560-0.

Wang, F., Kream, R. M., & Stefano, G. B. (2020). Long-term respiratory and neurological sequelae of COVID-19. *Medical Science Monitor 26*. https://doi.org/10.12659/msm.928996.

Wu, K., Fazal, F. M., Parker, K. R., Zou, J., & Chang, H. Y. (2020). RNA-GPS predicts SARS-COV-2 RNA residency to host mitochondria and nucleolus. *Cell Systems 11*(1), 102–108. https://doi.org/10.1016/j.cels.2020.06.008.

Xu, Z., Shi, L., Wang, Y., Zhang, J., Huang, L., Zhang, C., Liu, S., et al. (2020). Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *The Lancet Respiratory Medicine 8*(4), 420–422. https://doi.org/10.1016/s2213-2600(20)30076-x.

Zhang, Y., & Ma, Z. F. (2020). Impact of the COVID-19 pandemic on mental health and quality of life among local residents in Liaoning Province, China: a cross-sectional study. *International Journal of Environmental Research and Public Health 17*(7), 2381. https://doi.org/10.3390/ijerph17072381.