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LETTERS TO THE EDITOR

Are dopamine and serotonin involved in COVID-19 pathophysiology?



The whole world is being affected by COVID-19 caused by SARS-CoV-2, with unprecedented consequences on health, social and economic systems in all countries.

The COVID-19 pandemic is not only a threat to physical health but mental health as well.¹ In fact, scientific evidence is emerging on the potential direct effects of COVID-19 on mental health of people infected, as well as on the psychological impact on people quarantined, on patients with psychiatric disorders and on the health-care workforce.^{1,2}

Discussion on the first of these points (i.e. the direct effects of the infection on mental health) appears to be rather interesting. Clinical evidence is showing that patients with COVID-19 might experience short- and long-term mental health problems. Delirium, confusion, agitation, and altered consciousness, as well as depression, anxiety, traumatic stress, and insomnia, have been described not rarely in patients with COVID-19.^{1,2}

Putative aetiological mechanisms of the neuropsychiatric sequelae of coronavirus infection have a likely multifactorial basis but are still poorly established. The direct effects of viral infection on CNS, cerebrovascular disease, physiological impairments, the inflammatory response and the immune system reaction, medical interventions, social isolation, physical discomfort, the psychological impact of a novel severe and potentially fatal illness, concerns about infecting others, and clinical/social stigma, might be all involved in the aetiological process, independently or more likely synergistically.^{1,2}

Interestingly, it has been recently postulated that alterations of both the dopamine and serotonin synthetic pathways might be involved in COVID-19 pathophysiology.³ The possible involvement of these neurotransmitters is suggested by a significant link – based on similarities related to gene co-expression, co-regulation and function – between Angiotensin I Converting Enzyme 2 (ACE2, encoding the main receptor to SARS-CoV-2) and Dopa Decarboxylase (DDC, encoding the enzyme that catalyzes the biosynthesis of dopamine, serotonin and histamine). In fact, evidence shows that ACE2 and DDC co-express and co-regulate in non-neuronal cell types. Furthermore, it has been demonstrated that ACE2 receptors are highly expressed in dopamine neurons and that they are reduced in Parkinson's disease (characterized by dopamine deficiency).⁴ Hence, a

SARS-CoV-2-induced defective expression of ACE2 might be paralleled by a DDC dysfunction, with consequent potentially altered neurotransmitters' levels in COVID-19 patients.³

Therefore, short- and long-term neuropsychiatric disorders in COVID-19 patients could be explained – at least in part – by neurotransmission dysfunction/dysregulation.

Delirium, confusion, agitation, and sleep-wake disorders, for example, are commonly associated with alterations in melatonin (a product of serotonin), acetylcholine, dopamine, serotonin, and histamine. Furthermore, it has been demonstrated that viral infections with subsequent cytokine storm may contribute to suppressed serotonin and melatonin availability.⁵ Serotonin and norepinephrine are the biogenic amines most often associated with depression pathophysiology, but also dopamine play a significant role with data suggesting a reduced dopamine activity in depressed patients. Serotonin – together with norepinephrine and GABA – is one of the three major neurotransmitters associated with anxiety. Patients experiencing traumatic stress have chronically low levels of serotonin, and altered dopamine levels contributing to anhedonia, apathy, impaired attention, and motor deficits (when levels are low) and to psychotic symptoms and agitation (when levels are high).

It is obvious, however, that further experimental studies are necessary to elucidate the link between ACE2 and DDC during SARS-CoV-2 infection and to demonstrate the hypothetical alterations in dopamine, serotonin and other neurotransmitters in COVID-19 patients. More research is needed to explore the potential direct effects of COVID-19 on mental health, using both short- and long-term longitudinal investigations.

Ethical considerations

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Conflict of interest

None.

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Authors' contributions

LA conceived and drafted the article, FB revised it critically. LA and FB approved the final version of the manuscript.

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