Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Letter to the editor

Due to their anti-inflammatory, antioxidant and neurotrophic properties, second-generation antipsychotics are suitable in patients with schizophrenia and COVID-19

ARTICLE INFO

Keywords
SARS-CoV-2
Neuroinflammation
Astrocytes
Microglia
Nrf2
BDNF

One year after the coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a pandemic, there have been almost 3 million deaths reported, and more than 130 million people infected. In addition to gastrointestinal and hematological complications, approximately one-third of patients with COVID-19 have presented neurological or psychiatric symptoms, such as anxiety, depression, dementia, and psychosis, during their recovery period [1].

Psychosis is the core symptom of schizophrenia, which has neuro-inflammatory imbalance and its oxide-nitrosative consequences as prevalent neurobiological mechanisms (Fig. 1). Initial reports described increased risk for mortality in hospitalized COVID-19 patients with schizophrenia [2,3]. This phenomenon was attributed to the lack of adherence to public health measures (social distancing, hand washing, and the use of face masks) by patients, the limited availability of health services for patients with mental disease because of hospital saturations, or the delayed medical attention or treatment-seeking. Also, other comorbidity factors including obesity and diabetes which are prevalent in patients with schizophrenia [4], have been reported as risk factors to developing severe symptoms and increasing mortality in patients with COVID-19. However, neuroinflammation due to COVID-19 may be associated with disease outcomes in patients with schizophrenia. SARS-CoV-2 requires interaction with the angiotensin-converting enzyme 2 (ACE2) for cell docking, and the transmembrane serine protease 2 (TMPRSS2) for cell infection (Fig. 1). The nasal epithelium and the olfactory bulb may represent the gateway for SARS-CoV-2 to the brain [5], whose infection mechanisms are summarized in Fig. 1. Moreover, Wang et al., [6] demonstrated that apolipoprotein E4 (ApoE4), a glycoprotein involved in cholesterol metabolism highly expressed in the brain, increases SARS-CoV-2 infection susceptibility in neurons and astrocytes derived from human induced pluripotent stem cells (iPSC) and in brain organoids. In such a manner, the brain is an organ that is susceptible to SARS-CoV-2 infection, and neuroinflammation due to COVID-19 can generate neurologic or psychiatric symptoms or even aggravate them in diseases in which neuroinflammation is part of their pathophysiology, such as schizophrenia.

A couple of recent reports suggest that second-generation antipsychotic drugs (APDs) may prevent and protect against COVID-19 [7], and specifically aripiprazole seems to be a strong candidate [8]. Awaiting the replication of these results, and the elucidation of the mechanisms which contribute to the observed effects, Crespo-Facorro and colleagues suggest that second-generation APDs may have anti-inflammatory, antioxidant, and neurotrophic properties [9].

In recent years, it has been proposed that second-generation APDs, including risperidone, paliperidone, olanzapine, aripiprazole, and others, may enhance brain function in schizophrenia beyond their monoaminergic effects. This hypothesis is supported by the capability of these drugs to modulate microglia and astrocyte activation, reduce the levels of pro-inflammatory mediators, and enhance antioxidant systems such as the one regulated by nuclear factor E2-related factor 2 (Nrf2). Moreover, second-generation APDs stimulate neurotrophin activity, including brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) and enhance structural neuroplasticity in key brain regions for schizophrenia pathophysiology such as the prefrontal cortex (Fig. 1). The aforementioned effects have been demonstrated in vitro, in peripheral blood of patients with schizophrenia, and in the brain in animal models relevant for the study of the disease [9].

Despite second-generation APDs having lower rates of extrapyramidal side effects compared to first-generation APDs, these drugs still produce a myriad of side effects. Chronic treatment with second-generation APDs induces weight gain and alterations in carbohydrate metabolism, which lead to obesity and diabetes and generate cardiovascular complications, which are prevalent risk factors for severe outcomes and increase mortality in COVID-19. Moreover, clozapine (a second-generation APD) can induce neutropenia, which can be severe if the absolute neutrophil count (ANC) is not periodically assessed in patients [4]. Clozapine is the APD with the best efficacy outcome and the one prescribed for treatment-resistant schizophrenia which appears in approximately 34% of the patients [10]. Also, in respiratory tract infections, such as COVID-19, clozapine treatment may worsen the outcome by increasing the risk of pneumonia due to sialorrhea and subsequent aspiration [4]. However, since viral infections commonly
induce neutropenia, further studies must analyze whether neutropenia aggravates COVID-19 in patients with schizophrenia and how second-generation APDs treatment modulates it.

It is important to clarify that the COVID-19 pandemic may increase the possibilities of schizophrenia pharmacotherapy changes, interruptions, or suspension (because of medicine shortage, logistic delivery impediments, presence of side effects, etc.). In such a manner, clinicians must be careful in how the second-generation APDs dose is gradually reduced for these purposes, since this is crucial for the best outcome of the disease. In conclusion, COVID-19 and schizophrenia share neuroinflammation as relevant pathophysiological mechanisms, which may synergically worsen the outcome of both diseases. Second-generation APDs have anti-inflammatory, antioxidant, and neurotrophic properties which can ameliorate neuroinflammation and improve neuroplasticity. Thus, second-generation APDs seem to be suitable in patients with schizophrenia and COVID-19. However, chronic treatment with second-generation APDs is associated with the development of some risk factors for severe COVID-19 such as obesity and metabolic syndrome. This highlights the importance of adhering to the guidelines for the use of APDs, as well as constant monitoring of side effects, for effective pharmacotherapy.

Data availability

No data was used for the research described in the article.

Acknowledgements

Hiram Tendilla-Beltrán acknowledges CONACYT for Ph.D. scholarship. Gonzalo Flores acknowledges the “Sistema Nacional de Investigadores” for membership. Thanks to Prof. Robert Simpson for the English language edition.

References

[1] Taquet M, Luciano S, Geddes JR, Harrison PJ. Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA. Lancet Psychiatry 2021;8:130–40. https://doi.org/10.1016/S2215-0366(20)30462-4.
[2] Fond G, Pauly V, Orleans V, Antonini F, Fabre C, Sanz M, et al. Increased in-hospital mortality from COVID-19 in patients with schizophrenia. Encephale 2020; 1:1–11. https://doi.org/10.1016/j.encep.2020.07.003.
[3] Li L, Li F, Fortunati F, Krystal JH. Association of a prior psychiatric diagnosis with mortality among hospitalized patients with coronavirus disease 2019 (COVID-19) infection. JAMA Netw Open 2020;3:e2023282. https://doi.org/10.1001/jamanetworkopen.2020.23282.
[4] Kahn RS, Sommer IE, Murray RM, Meyer-Lindenberg A, Weinberger DR, Cannon TD, et al. Schizophrenia. Nat Rev Dis Prim 2015;1:15067. https://doi.org/10.1038/nrdp.2015.67.
[5] Brann DH, Tsukahara T, Weinreb C, Lipovic M, Van Der Beke K, Gong B, et al. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. Sci Adv 2020;6:1–20. https://doi.org/10.1126/sciadv.abc5801.
[6] Wang C, Zhang M, Garcia G, Tian E, Cui Q, Chen X, et al. ApoE-Isotype-Dependent SARS-CoV-2 Neurotropism and Cellular Response. Cell Stem Cell 2021;28. https://doi.org/10.1016/j.stem.2020.12.018. 331-342.e5.
[7] Canal-Rivero M, Catalán-Barragán R, Rubio-García A, Garrido-Torres N, Crespo-Faccoro B, Ruiz-Veguilla M. Lower risk of SARS-CoV2 infection in individuals with severe mental disorders on antipsychotic treatment: a retrospective epidemiological study in a representative Spanish population. Schizophr Res 2021;229:53–60. https://doi.org/10.1016/j.schres.2021.02.002.
[8] Crespo-Faccoro B, Ruiz-Veguilla M, Vázquez-Bourgon J, Sánchez-Hidalgo AG, Garrido-Torres N, Cimeno JM, et al. Aripiprazole as a candidate treatment of COVID-19 identified through genomic analysis. Front Pharmacol 2021;12. https://doi.org/10.3389/fphar.2021.646701.
[9] Tendilla-Beltrán H, Sánchez-Islas N, Marina-Ramos M, Leza JC, Flores G. The prefrontal cortex as a target for atypical antipsychotics in schizophrenia, lessons of neurodevelopmental animal models. Prog Neurobiol 2021;199:101967. https://doi.org/10.1016/j.pneurobio.2020.101967.
[10] Potkin SG, Kane JM, Correll CU, Lindenmayer JP, Agid O, Marder SR, et al. The neurobiology of treatment-resistant schizophrenia: paths to antipsychotic
resistance and a roadmap for future research. NPJ Schizophr 2020;6. https://doi.org/10.1038/s41537-019-0090-z.

Hiram Tendilla-Beltrán a,b, Gonzalo Flores a,*

a Instituto de Fisiología, Benemérita Universidad Autónoma de Puebla (BUAP), Puebla, Mexico

b Escuela Nacional de Ciencias Biológicas (ENCB), Instituto Politécnico Nacional (IPN), CDMX, Mexico

* Corresponding author at: Instituto de Fisiología, Benemérita Universidad Autónoma de Puebla, 14 sur 6301, 72570 Puebla, Mexico.
E-mail addresses: gonzaloflores56@gmail.com, gonzalo.flores@correo.buap.mx (G. Flores).