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.

Psychiatry Research 291 (2020) 113220

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Letter to the Editor

Psychotropics drugs with cationic amphiphilic properties may afford some protection against SARS-CoV-2: A mechanistic hypothesis

As of 16 May 2020, the World Health Organization reports a total of 4 396 392 cases of 2019-nCoV infection, and 300 441 deaths. A rapid response to this pandemic would be greatly helped by the possibility to repurpose old drugs as novel antiviral medications. Since the beginning of the COVID-19 outbreak, psychiatrists from Sainte Anne hospital (France) have observed a lower prevalence of symptomatic and severe forms of COVID-19 infections in psychiatric patients (~4%) compared to healthcare professionals (~14%). Similar observations have been noted in other psychiatric units in France and abroad. Even if healthcare professionals are more likely to be exposed to SARS-CoV-2, the prevalence observed in psychiatric patients is likely low as compared to the general population since the prevalence was forecasted to be 9.9% (range: 6.6–15.7) in Ile-de-France, which includes Paris, by 11 May 2020 (Salje et al., 2020). The hypothesis that psychiatric patients could be protected from severe forms of COVID-19 by their psychotropic treatments has been put forward by Plaze and co-workers (Plaze et al., 2020). Chlorpromazine is a phenothiazine derivative widely used in clinical routine in the treatment of acute and chronic psychoses. The repositioning of chlorpromazine as an anti-SARS-CoV-2 drug offers an alternative and rapid strategy to alleviate the virus propagation and the infection severity and lethality. Chlorpromazine inhibits clathrin-mediated endocytosis and is a cationic amphiphilic drug (CAD) and it can be speculated that this property may play a role in the protection of psychiatric patients. CADs such as numerous antipsychotics (such as chlorpromazine, promethazine, trifluoperazine, thioridazine, perphenazine, fluphenazine, prochlorperazine, haloperidol, cis-(Z)-flupentixol), antidepressants (such as imipramine, trimipramine, amitriptyline, clomipramine, nortriptyline, sertraline, fluoxetine, paroxetine), antiarrhythmics (such as amiodarone, bepridil, verapamil) and other drugs used against SARS-CoV-2 such as hydroxychloroquine or azithromycin are characterized by a hydrophobic aromatic ring or ring system and a hydrophilic side chain containing an ionizable amine functional group. Since some psychotropic drugs especially antipsychotics and antidepressants are endowed with this property, it is not surprising that psychiatric patients may be protected from symptomatic SARS-CoV-2 infections. Thus, the field of psychiatry could provide innovative therapeutic approaches to fight COVID-19. CADs have the ability to accumulate inside cells affecting several structures/functions hijacked by viruses during infection. In their review, Salata and co-workers (2017) summarized the CADs' chemical properties and effects on the cells and reported the main FDA-approved CADs that have been identified so far as potential antivirals in drug repurposing studies (Salata et al., 2017). Although there have been concerns regarding the efficacy and the possible side effects (especially risk of Torsades de Pointes (TdP) and phospholipidosis) of the off-label use of CADs as antivirals, they seem to represent a promising starting point for the development of broad-spectrum antiviral strategies. Further knowledge about their mechanism of action is required to improve their antiviral activity and to reduce the risk of side effects (hydroxychloroquine, azithromycin, and chlorpromazine are classified as having Known Risk of TdP). Coronaviruses are enveloped, non-segmented positive sense RNA viruses. Their surface displays club-shaped protrusions made by trimers of the spike (S) protein. The initial attachment of the virion to the host cell is initiated by interactions between the S-protein and its receptor, which varies according to the specific virus. The S-protein/receptor interaction is the primary determinant for a coronavirus to infect a host species and governs the tissue tropism of the virus. Following receptor binding, the virus is taken up by receptor-mediated endocytosis, ending in an acidic endosomal compartment where the S-protein undergoes an acid-dependent proteolytic cleavage by cathepsin L. The S-protein then triggers the mixing of viral and endosomal membranes, causing the release of the viral genome into the cytoplasm. A mildly acidic pH environment in late endosomes/lysosomes seems to be important, since infection can be blocked by lysosomotropic agents such as chloroquine (Aimo et al., 2020). Because of their structure, lysosomotropic CADs accumulate into acidic compartments such as late endosomes/lysosomes, reducing their luminal acidity, altering the trafficking of membrane components and inducing in several cell types, for example, alveolar macrophages, a Niemann–Pick C-like phenotype. This may affect cell activities important for an efficient viral internalization, such as partial hydrolysis of viral surface proteins, macropinocytosis (inhibited by imipramine for example – Lin et al. (Lin et al., 2018)) or micropinocytosis, the organization of the membrane invagination systems, and the vesicular transport of material to the lysosomes. For a review of the mechanism of amiodarone (and thus likely other CADs) the reader may see Aimo and co-workers' s paper (Aimo et al., 2020). It has been proposed that ether-à-gogo- related gene hERG channel blockers and phospholipidosis inducers (hydroxychloroquine, azithromycin for example) share a large chemical space (Sun et al., 2013). Thus, a challenge would be to search for CADs without marked activity at this potassium channel. Although the antiviral activity of CADs is most likely due to interference with the endocytic pathway (Aimo et al., 2020), further mechanisms cannot be excluded. The assessment of the therapeutic potential of FDA-approved CADs in cell cultures and animal models may be considered, then the evaluation of the most promising drugs in human patients could be performed in the near future. Since imipramine has been used for decades on millions of patients, its safety profile is well known, it induces a lower risk of TdP than chlorpromazine, and it appears to be a good candidate for phase III trials. Notably, as stated by (Aimo et al., 2020) CADs appear to be not strong antivirals, and it may be speculated that they are more effective with low viral loads and at the start of infection, when virus entry into target cells is the dominant step. Further knowledge about the mechanism of action of CADs is required to improve their antiviral activity and to reduce the risk of side effects.

https://doi.org/10.1016/j.psychres.2020.113220
Received 17 May 2020; Received in revised form 8 June 2020; Accepted 9 June 2020
Available online 10 June 2020
0165-1781/

Author's contribution

JMV designed the review, appraised the quality of included papers, and drafted the manuscript.

Declaration of Competing Interest

The author declares that he has no competing interests.

References

Aimo, A., Baritussio, A., Emdin, M., Tascini, C., 2020. Amiodarone as a possible therapy for coronavirus infection. Eur. J. Prev. Cardiol. https://doi.org/10.1177/2047487320919233. 2047487320919233.

Lin, H.-P., Singla, B., Ghoshal, P., Faulkner, J.L., Cherian-Shaw, M., O'Connor, P.M., She, J.-X., Belin de Chantemele, E.J., Csányi, G., 2018. Identification of novel macropinocytosis inhibitors using a rational screen of Food and Drug Administration-approved drugs. Br. J. Pharmacol. 175, 3640–3655. https://doi.org/10.1111/bph.14429.

Plaze, M., Attali, D., Petit, A.-C., Blatzer, M., Simon-Loriere, E., Vinckier, F., Cachia, A., Chrétien, F., Gaillard, R., 2020. [Repurposing of chlorpromazine in COVID-19 treatment: the reCoVery study]. Encephale. https://doi.org/10.1016/j.encep.2020.04.010.

Salata, C., Calistri, A., Parolin, C., Baritussio, A., Palù, G., 2017. Antiviral activity of cationic amphiphilic drugs. Expert. Rev. Anti. Infect. Ther. 15, 483–492. https://doi.org/10.1080/14787210.2017.1305888.

Salje, H., Tran Kiem, C., Lefrancq, N., Courtejoie, N., Bosetti, P., Paireau, J., Andronico, A., Hozé, N., Richet, J., Dubost, C.-L., Le Strat, Y., Lessler, J., Levy-Bruhl, D., Fontanet, A., Opatowski, L., Boelle, P.-Y., Cauchemez, S., 2020. Estimating the burden of SARS-CoV-2 in France. Science. https://doi.org/10.1126/science.abc3517.

Sun, H., Xia, M., Shahane, S.A., Jadhav, A., Austin, C.P., Huang, R., 2013. Are hERG channel blockers also phospholipidosis inducers? Bioorg. Med. Chem. Lett. 23, 4587–4590. https://doi.org/10.1016/j.bmcl.2013.06.034.

Jean-Marie Vaugeois[*,a,b]

[a] *Normandie University, université de Rouen, université de Caen, ABTE, Rouen 76000, France*

[b] *Département de Pharmacie, UFR Santé, 22, boulevard Gambetta, 76183 Rouen cedex 1, France*

E-mail address: jean-marie.vaugeois@univ-rouen.fr.

[*] Corresponding author at: Laboratoire ABTE, Equipe Toxemac EA 4651, UFR Santé, Département de Pharmacie, 22, boulevard Gambetta, 76183 Rouen cedex 1, France.