Lithium as a candidate treatment for COVID-19: Promises and pitfalls

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Abstract

The pandemic of respiratory illness caused by a novel coronavirus (SARS-nCoV-2) is a global health crisis. Despite numerous preliminary results, there is as yet no treatment of proven efficacy for this condition. In this context, the pharmacological properties of lithium, better known as a treatment for mood disorders, merit closer examination. Lithium has shown in vitro efficacy at inhibiting the replication of coronaviruses responsible for gastrointestinal and respiratory diseases in animals. It has immunomodulatory properties that may be of additional benefit in moderating the host inflammatory response to the novel coronavirus (SARS-CoV-2). Furthermore, there is evidence that lithium may exert a protective action against upper respiratory infections and influenza-like illnesses in patients taking it for other indications. These promising reports must be balanced against the narrow therapeutic index and high risk of toxicity associated with lithium therapy, its documented interactions with several commonly used drugs, and the absence of evidence of its efficacy against coronaviruses responsible for human disease. Nevertheless, naturalistic studies of the risk of COVID-19 in patients already receiving lithium could provide indirect evidence of its efficacy, and understanding the putative antiviral and immune-regulatory mechanisms of lithium in models of SARS-CoV-2 infection may provide leads for the development of safer and more effective treatments with a specific action against COVID-19.

KEYWORDS

COVID-19, lithium, nCoV-2
A variety of treatments, including viral replication inhibitors, chloroquine and hydroxychloroquine, azithromycin, and immunotherapies, are being investigated as therapeutic options for COVID-19. Despite initial promising reports, there is insufficient evidence to recommend any of these, as well as substantial concerns about drug toxicity in some cases (Chary, Barbuto, Izadmehr, Hayes, & Burns, 2020). Given these limitations, as well as the time frame required for development of an effective vaccine, it is important to explore other therapeutic options (Ebrahimi, 2020).

Lithium salts, conventionally used in the treatment of bipolar disorder and related conditions, could represent one such alternative. The pharmacodynamics of lithium are complex and involve effects on genes related to the downstream effects of neurotransmitter cascades, as well as neural plasticity (Rybakowski, 2020). However, lithium has also been documented to moderate the immune-inflammatory activation seen during episodes of mood disorder, including the normalization of cytokine levels (Rybakowski, 2000; van den Ameele et al., 2016). In addition, lithium has been documented to have direct anti-viral effects. A close examination of these two properties reveals a conjunction of actions that may be of particular significance in treating infection with SARS-nCoV-2.

Evidence for a direct effect of lithium against some members of the coronavirus family has accumulated over the past decade. Initially, lithium was thought to exert an antiviral effect mainly on DNA viruses, particularly herpes simplex viruses (Bach, 1987; Skinner, Hartley, Buchan, Harper, & Gallimore, 1980). This was confirmed by evidence that lithium therapy, at doses similar to those used in the maintenance treatment of bipolar disorder, was effective in treating recurrent genital herpes (Amsterdam, Maislin, Potter, & Giuntoli, 1990) and labial herpes (Amsterdam, Maislin, & Rybakowski, 1990). Similarly, topical application of lithium succinate proved efficacious in some patients with anogenital warts caused by the human papillomavirus (Ward et al., 1997). Subsequently, lithium was shown to significantly reduce the rates of influenza-like illnesses in patients with mood disorders; this effect, like its effects against herpes, was specific to lithium and was not seen with antidepressants (Amsterdam, Garcia-Espana, & Rybakowski, 1998). This raised the possibility that lithium could possess meaningful in vivo activity against RNA viruses. More recent research suggests that lithium has at least in vitro activity against several coronaviruses, including both gastrointestinal and respiratory pathogens (Harrison et al., 2007; Li et al., 2018; Ren et al., 2011). The putative mechanisms of this antiviral action may involve the inhibition of RNA polymerases (Harrison et al., 2007) or a protective action against apoptosis triggered by viral infection (Ren et al., 2011).

From the perspective of immune modulation, lithium appears to exert an inhibitory action on NF-κB (Troib & Azab, 2015) which plays a key role in the initiation of the “cytokine storm” triggered by infection with SARS-nCoV-2. It has also been shown to reduce levels of TNF-α and IL-6, which are also crucial parts of this pathway, in an animal model of sepsis (Albayrak et al., 2013). Furthermore, lithium appears to inhibit the process by which IL-6 activates the transcription factor STAT-3 in an animal model of joint inflammation (Minashima, Zhang, Lee, & Kirsch, 2014), which means that it could potentially interrupt the self-reinforcing inflammatory cascade described above. At least some of these effects appear to be related to the inhibitory effects of lithium on the enzyme glycogen synthase kinase-3-beta (GSK-3β) (Beurel, Michalek, & Jope, 2010; Wang et al., 2013), which has also been identified as a molecular target for the action of chloroquine and hydroxychloroquine in reducing inflammation triggered by SARS-nCoV-2 (Embi, Ganesan, & Sidek, 2020). Besides its effects on this particular pathway, lithium also seems to have more widespread anti-inflammatory effects, including the inhibition of interleukin-1 beta (IL-1β) production and the reduction of cyclooxygenase-2 expression (Nassar & Azab, 2014). Taken together, these findings suggest that lithium may exert a beneficial effect on the “inflammatory storm” that seems to underlie some of the more severe manifestations of COVID-19.

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These promising indicators, summarized in Table 1, must, however, be weighed against several potential drawbacks of lithium therapy. First, lithium has a narrow therapeutic index and a wide range of drug interactions—including interactions with some antiviral drugs—that place the patient at risk of lithium toxicity (Finley, 2016). Second, the concentrations at which lithium exerts an antiviral effect in vitro are several times higher than the acceptable therapeutic levels (Li et al., 2018; Ren et al., 2011), meaning that achieving lithium levels sufficient to inhibit viral replication may not be possible in human patients; however, such a limitation may not apply to its immunomodulatory properties, and there is at least preliminary in vivo evidence for an antiviral effect of lithium at tolerable therapeutic doses (Amsterdam, Maislin, Potter, & Giuntoli, 1990; Amsterdam, Maislin, & Rybakowski, 1990). This may be due to the fact that lithium levels in
TABLE 1  Potential anti-viral and immunomodulatory mechanisms of lithium relevant to SARS-CoV-2 infection

| Action                  | Mechanism                                                                 | References                                                                 |
|------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Antiviral effects      | Inhibition of viral RNA polymerase, probably related to blockade of co-factor phosphorylation through inhibition of GSK-3β | Harrison et al., 2007; Asenjo et al., 2008                                  |
|                        | Protection of host cells from apoptosis triggered by viral infection       | Ren et al., 2011                                                           |
| Immunomodulatory effects | Inhibition of NF-κB                                                        | Troib & Azab, 2015                                                         |
|                        | Inhibition of IL-6 induced activation of STAT-3, perhaps mediated through inhibition of GSK-3β | Beurel et al., 2010; Wang, Zhang, Li, et al., 2013; Minashima et al., 2014 |
|                        | Inhibition of IL-1β production                                             | Nassar & Azab, 2014                                                       |
|                        | Reduction in cyclooxygenase-2 expression                                   | Nassar & Azab, 2014                                                       |

Abbreviations: RNA, ribonucleic acid; GSK-3β, glycogen synthase-3 beta; NF-κB, nuclear factor kappa B; STAT-3, signal transducer and activator of transcription 3; IL-6, interleukin-6; IL-1β, interleukin-1 beta.

REFERENCES

Adhikari, S. P., Meng, S., Wu, Y. J., Mao, Y. P., Ye, R. X., Wang, Q. Z., … Zhou, H. (2020). Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: A scoping review. Infectious Diseases of Poverty, 9, 29. https://doi.org/10.1186/s40249-020-00646x

Albayrak, A., Halici, Z., Polat, B., Karakus, E., Cadirci, E., Bayir, Y., … Atamanalp, S. S. (2013). Protective effects of lithium: A new look at an old drug with potential antioxidative and anti-inflammatory effects in an animal model of sepsis. International Immunopharmacology, 16, 35–40. https://doi.org/10.1016/j.intimp.2013.03.018

Amsterdam, J. D., Garcia-Espana, F., & Rybakowski, J. K. (1998). Rates of influenza-like illness in patients with affective illness. Journal of Affective Disorders, 47, 177–182.

Amsterdam, J. D., Maislin, G., Potter, L., & Giuntoli, R. (1990). Reduced rate of recurrent genital herpes infections with lithium carbonate. Psychopharmacology Bulletin, 26, 343–347.

Beurel, E., Michalek, S. M., & Jope, R. S. (2010). Innate and adaptive immune responses regulated by glycogen synthase kinase-3 (GSK-3). Trends in Immunology, 31, 24–31. https://doi.org/10.1016/j.it.2009.09.007

Bach, R. O. (1987). Lithium and viruses. Medical Hypotheses, 23, 157–170.

Beurel, E., Michalek, S. M., & Jope, R. S. (2010). Innate and adaptive immune responses regulated by glycogen synthase kinase-3 (GSK-3). Trends in Immunology, 31, 24–31. https://doi.org/10.1016/j.it.2009.09.007

Chary, M., Barbuto, A. F., I zadmehr, S., Hayes, B. D., & Burns, M. M. (2020). COVID-19: Therapeutics and their toxicities. Journal of Medical Toxicology. (Online ahead of print.). https://doi.org/10.1007/s13181-020-00777-5

Ebrahim, S. A. (2020). Noscapine, a possible drug candidate for attenuation of cytokine release associated with SARS-CoV-2. Drug Development Research, 81(7), 765–767. https://doi.org/10.1002/ddr.21676

Embi, M. N., Ganesan, N., & Sidek, H. M. (2020). Is GSK3β a molecular target of chloroquine treatment against COVID-19? Drug Discoveries & Therapeutics, 14, 107–108. https://pubmed.ncbi.nlm.nih.gov/32321878

Finley, P. R. (2016). Drug interactions with lithium: An update. Clinical Pharmacokinetics, 55, 925–941. https://doi.org/10.1007/s40262-016-0370-y

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CONFLICT OF INTEREST

The author reports no current or potential conflict of interest.

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