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Lithium salts as a possible therapeutic option for SARS CoV 2 infection.

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Abstract

SARS-CoV-2 causes a severe respiratory disease (COVID-19) characterized by marked deregulation of the immune system, which provokes a hyper-inflammatory state. With the uncertainties regarding the efficacy of vaccines against new variants, there is an urgent need for repurposing current drugs, which have a mechanism of action that justifies their use for the treatment of COVID-19. To summarize the current evidence on the mechanisms of action of lithium salts on viral infections and the immune system. Google Scholar and PubMed were used to the key words "lithium," "immune system," "inflammation," "antiviral," "SARS-CoV-2," and "coronavirus." We identified 78 papers: 52 were original works (clinical trials, descriptive studies or preclinical assessments), 23 were systematic reviews of related topics, two government reports and one book. Lithium has shown direct antiviral effects by inhibiting the *in vitro* replication of several types of viruses. It may also have indirect antiviral effects by enhancing the antiviral response which is mediated by inhibition of the expression of programmed cell-death protein 1 in cells from innate and acquired immunity. Moreover, lithium reduces inflammation by interfering with the production of pro-inflammatory cytokines. A small study in patients with COVID-19 was conducted in Spain with remarkable outcomes, but no preclinical specific evaluation was found. Lithium is a promising candidate for the treatment of COVID-19. Its use could have great relevance in the treatment of patients with severe cytokine storm. Preclinical and clinical trials are needed to assess the therapeutic capacity of lithium salts in the treatment of COVID-19 patients.

Keywords: Lithium, Immune system, Inflammation, Antiviral, SARS-CoV-2, and Coronavirus.

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Background

SARS-CoV-2 has challenged the health systems worldwide since December 2019. This virus causes a severe respiratory disease (COVID-19) characterized by marked deregulation of the immune system with over-production of pro-inflammatory cytokines (cytokine storm), in particular IL-6 and TNFα [1], and an increased expression of programmed cell death protein 1 (PD-1), an inhibitory receptor [2], particularly in natural killer (NK) and CD8+ T-cells, which are essential for antiviral defense.

The development of specific drugs is slow and time consuming. Drugs initially produced for other human diseases, which could generate some benefits in the treatment of patients with COVID-19 due to their mechanism of action, have obtained special permission for use in treating COVID-19 (*i.e.* "compassionate treatment"). This is the case with remdesivir [3], chloroquine [4], lopinavir/ritonavir [5], and tocilizumab [6].

In Cuba, Itolizumab and Jusvinza have obtained special authorization for the treatment of COVID-19. These drugs have immunomodulatory properties and are currently in an advanced clinical phase for the treatment of psoriasis and rheumatoid arthritis (RA). The first is a humanized monoclonal antibody, developed by the Center for Molecular Immunology, which reduces the expression of intracellular proteins involved in the activation of T cells and inhibits the production of pro-inflammatory cytokines such as IFN-γ, IL-6, and TNF-α [7]. These characteristics justify its use in reducing the effects of cytokine release syndrome in COVID-19. Itolizumab reduced the risk of dying in patients with moderate and severe signs compared to control patients with the same degree of disease severity. It reduces the level of IL-6 or blocks its over-secretion such that most patients show pulmonary improvement and are rapidly discharged from the intensive care unit [7].

Jusvinza is an immunomodulatory peptide with anti-inflammatory properties that was developed at the Center for Genetic Engineering and Biotechnology for the treatment of autoimmune diseases, specifically RA [8]. After authorization for the treatment of critical patients with COVID-19, it was observed that patients began to present clinical, gasometric, and radiological improvements; after 48 h of treatment, the levels of pro-inflammatory cytokines involved in the cytokine storm (TNFα, IL-1, and IL-6) were significantly reduced during the course of treatment [9].

Treatments for COVID-19 have focused on four main objectives: neutralizing/eliminating the virus, enhancing the defense mechanisms of the immune system, reducing the consequences of immune deregulation, and/or treating the symptoms/signs and their consequences. With the uncertainties regarding the efficacy of vaccines against new variants, there is an urgent need for repurposing of current drugs, which have a mechanism of action that justifies their use for the treatment of this disease. This article reviews the mechanisms of action of lithium, suggesting its potential for COVID-19 treatment.

Methods

We use Google Scholar and PubMed search tools with the key words "lithium," "immune system," "inflammation," "antiviral," "SARS-CoV-2," and "coronavirus." The searches identified 634 articles, 561 of which were related with lithium's mechanisms of action. We included original articles that provided evidence of the antiviral and immunomodulatory effects of lithium salts. We identified 78 papers: 52 were original works (clinical trials, descriptive studies or preclinical assessments), 23 were systematic reviews of related topics, two government reports and one book.

Lithium salts

Lithium salts are the gold standard for the treatment of bipolar disorder, and their use in medicine dates back to the middle of the 19th century [10]. In psychiatry, lithium was used as an anticonvulsant and hypnotic treatment in 1870 [11], and as a specific treatment for mania in 1949 after observing its sedative properties in guinea pigs [12]. In addition, lithium has been described as an antiviral [13], immunomodulatory [14], and neuroprotective drug [15,16]. Its antiviral properties can be direct or indirect [17- 21]. The direct effect is by interfering with viral replication, and its indirect effect is through the downregulation of PD-1, which enhances the antiviral response. Its mechanisms of action have been studied both *in vitro* and *in vivo*.

Lithium inhibits glycogen synthase kinase-3 (GSK-3)

Lithium is an alkali metal (group IA of the periodic table) that is not found free in nature. The pharmaceutical forms used have been lithium salts (chloride, citrate, bromide, sulfate, and carbonate). Lithium chloride has been used less frequently because it is hygroscopic and less tolerated. In contrast, lithium carbonate is used worldwide [22]. The mechanism of action of lithium is complex because it interferes with several signaling pathways and modulates the expression of multiple genes involved in important cellular processes.

Although its exact mechanism of action has not yet been fully elucidated, one hypothesis suggests that lithium is a competitive inhibitor of magnesium (Mg^{2+}) [23]. Lithium and magnesium have similar atomic radii (0.076 and 0.072 nm, respectively), which could explain many of the biochemical effects of lithium because Mg^{2+} is a co- factor of multiple enzymes.

Lithium salts inhibit important enzymes, including inositol monophosphatase [24],

but their ability to inhibit GSK-3 is most closely related to its broad spectrum of therapeutic properties. GSK-3 is a constitutive enzyme important in several biological processes, being the point of convergence of several signaling pathways and it regulates the activity of more than 50 substrates [25]. It participates in glycogenic metabolism, cell cycle, apoptosis, and gene transcription. At the immunological level, inhibition of cytosolic and/or nuclear GSK-3 increases the expression of T-box transcription factor TBX21, also called T-box expressed in T cells (Tbet), which in turn suppresses PD-1 transcription and expression in activated T and B lymphocytes, particularly CD8 T cells [26]. Lithium is the first GSK-3β natural inhibitor to be described [27].

Lithium's antiviral effects

The antiviral properties of lithium have been studied since 1980 [17]. *In vitro* experiments have shown that it can inhibit the replication of different viral types, including herpes viruses [17], coxsackie viruses [18,19], hepatitis C virus (HCV) [20], and coronaviruses [21]. Several descriptive studies have shown that patients receiving lithium treatment have reduced rates of herpes virus [13,28] and influenza virus infections [29,30].

Although the mechanisms by which lithium exerts these antiviral effects are not yet clear, two different pathways can be exposed, both related to the inhibition capacity of GSK-3. When studying the consequences of the *in vitro* inhibition of this enzyme by lithium salts on HCV replication, a significant reduction in the number of copies of the virus in the supernatant of treated cells has been demonstrated [20]. It has been proposed that GSK-3 is directly involved in virion maturation by participating in the assembly and release of viral particles through lipid biosynthesis [20].

Coronaviruses require host GSK-3 activity for survival. This enzyme phosphorylates the nucleocapsid glycoprotein (N) [31], an essential step in the generation of long subgenomic and genomic mRNAs that encode structural proteins in the cell cytosol [32]. This could also be extrapolated to the SARS-CoV-2. Therefore, GSK-3 inhibitors, such as lithium, can directly interfere with viral replication [33].

On the other hand, PD-1 is a cell surface receptor expressed transiently in multiple cells of the immune system, including T and B lymphocytes [34], macrophages [35], NK cells [36] and dendritic cells [37]. It functions as an immune checkpoint and plays an important role in the negative regulation of the immune system [38]. PD-1 is not expressed in naive cells, but only in lymphocytes activated by cell receptors [39]. If the activating antigen is removed, PD-1 expression decreases rapidly. If the activating antigen persists, PD-1 expression remains high and sustained [40]. The inhibitory effect of PD-1 on the immune system occurs through a mechanism that promotes apoptosis of antigen-specific activated T cells in lymph nodes, reducing CD8+ T-cell responses, and possibly by reducing apoptosis of regulatory T cells [41,42].

Blockade of PD-1 is known to increase the self-renewal and proliferation of stem- like CD8 T-cells in lymph nodes, increasing the effect of cytotoxic T-lymphocytes

(CTL) on infections and cancer [43-45]. Various transcription factors and some enzymes that participate in upstream signaling pathways regulate PD-1 expression in activated T cells [46]. In 2016, Taylor *et al*. demonstrated that GSK-3 inhibition enhances Tbx21 transcription, which represses PD-1 transcription and enhances CTL function [26]. Therefore, GSK-3 inhibitors, such as lithium, may have indirect antiviral effects by enhancing the antiviral CTL activity.

Immunomodulatory effects

The first observation of the influence of lithium on the immune system was described more than 40 years ago [47]. Murphy *et al*. noticed that patients treated with lithium salts had an increased number of blood leukocytes, which is why some clinicians even used it in patients with leukopenia [48].

Lithium is an anti-inflammatory drug. Several studies have investigated the effects of lithium on the production of several pro-inflammatory cytokines, such as IL-6, IL- 4, IFN-γ, IL-1β, and TNF-α [49-53]. This could have a great relevance in marked pro- inflammatory states such as the 'cytokine storm' developed in patients with severe presentation of COVID-19. In addition, lithium can be involved in the production of anti- inflammatory cytokines, such as IL-10 [54-58].

Meanwhile, under certain experimental conditions, lithium exhibits pro-inflammatory properties [59,60]. In the latter, the research subjects were healthy, under baseline conditions (without infection or provoked inflammatory state). From the foregoing, it can be inferred that the actions of lithium (and GSK-3) depend on the context (microenvironment) in which the target cell develops.

Considering all the above, lithium could be used in the treatment of COVID-19 as it has a direct antiviral action (inhibits coronavirus replication), an indirect antiviral action that enhances the antiviral T response (inhibiting PD-1) [26], and also immunomodulatory properties (decreased production of IL-6, IL1β, and increased production of IL-10), three significant attributes against SARS-CoV-2. Many authors have suggested lithium treatment for COVID-19 patients [21, 33, 61,62], and even a small study in humans was carried out in Spain, in what could be considered a "proof of concept". Spuch *et al*. [63] indicated lithium carbonate in six SARS-CoV-2 positive patients with severe presentation of the illness. All had high levels of D-dimer and C-reactive protein, as well as lymphocytopenia and neutrophil/lymphocyte ratio (NLR) above four that indicated a marked hyperactive inflammation status.

The study showed the anti-inflammatory properties of lithium, since in all treated patients the levels of C-reactive protein decreased significantly, the levels of lymphocytes increased and therefore the NLR value decreased.

Pharmacokinetics

Oral lithium is completely absorbed from the gastrointestinal tract, with maximum plasma concentrations occurring within 2-4 h after administration [64]. It is widely distributed throughout the body's tissues and fluids, including bones, red blood cells, brain, saliva, and thyroid glands [65,66]. Lithium crosses the placenta, permitting similar maternal and fetal serum concentrations [67].

Lithium has biphasic elimination with an α half-life of 5 h and a β-one of 18 h. Lithium is filtered by the glomeruli, and approximately 80% of it is reabsorbed in the renal tubules [68]. Less than 1% is excreted in the feces. Clearance is proportional to its serum concentration, and ~ 50% of a single dose is excreted within 24 h [68]. This is constant in each individual, but depends on age and salt intake. Food does not affect the bioavailability of lithium because it does not bind to plasma proteins; it is not metabolized, and its elimination is mainly renal [66].

Adverse effects

Mild side effects can be observed even when serum lithium levels remain below 1 mmol/L. The most common side effects are post-absorbent symptoms, which are believed to be associated with a rapid increase in serum levels. They include nausea, abdominal pain, vomiting, diarrhea, muscle weakness, drowsiness, and light- headedness, and often subside after stabilization of therapy. Its incidence can be reduced if the drug is ingested with large meals, such as lunch and/or dinner [69]. Lithium carbonate tablets should be swallowed in whole and should not be broken or chewed. It is important to consume sufficient fluid (at least 2 L) and have a well- balanced sodium intake. The most common and persistent adverse reactions are fine tremor of the hands that do not respond to anti-parkinsonian drugs, and occasionally, fatigue, thirst, and polyuria [67].

Toxicity

The main cause of the low use of lithium, despite its promising mechanisms of action, is the concern of health professionals about its toxic effects. The main signs of lithium intoxication are nausea, vomiting, confusion, seizures, electrocardiographic changes, and kidney failure [67]. Generally, serum lithium concentrations are measured to verify patient compliance and prevent intoxication in patients with prolonged treatment. However, some important aspects need to be considered. Most, if not all, cases of lithium intoxication have been associated with prolonged use (for more than 10-15 years) and suicide attempts. Nevertheless, the mortality rate among patients with intoxication is less than 1% [70,71].

The events associated with the toxicity of lithium salts could be minimized with short treatments (in patients with bipolar disorders, their sustained use over time is important or essential, but in new therapeutic applications, this does not have to be the case). In addition, it is important to keep in mind that some patients have issues related to excess alcohol consumption, for whom treatment with lithium carbonate should be avoided (or at least adapted). Among these are patients with severe renal and cardiovascular diseases, dehydration, or concomitant therapy with diuretics [72]. Patients with respiratory infections (among others) tend to be mildly dehydrated, so the dose should be readjusted in patients with moderate or severe presentation of this infection (they require a lower dose) [72].

Lithium was approved by the Food and Drug Administration (FDA) in 1970 [73]. Some European countries had approved its clinical use years before [74]. In Cuba, it has been used for years in the treatment of affective disorders, and lithium clinics were created in 1982 by the National Group of Psychiatry.

Lithium as a possible therapeutic option for COVID-19. Discussion

The evidence reviewed suggests that the use of lithium salts could play an important role in the treatment of COVID-19, even in severe cases where immune deregulation is already in place. Lithium has some benefits that make it an electable drug for this disease.

First, three highly relevant action mechanisms in the therapeutic approach of COVID- 19 take place at the same time: it directly inhibits the replication of various types of viruses, including some coronaviruses, and indirectly enhances the antiviral mechanisms of the innate and acquired immune system. It also has an anti- inflammatory action, which can be of great relevance in a disease characterized by triggering a hyper-inflammatory state.

Second, lithium carbonate is a generic drug that is already available in markets worldwide, and there is a significant experience in its clinical use. It has a low cost of production, storage, and transportation, making it an affordable option. Certainly, this does not make it very appealing to pharmaceutical companies.

Third, regardless its risk of toxicity, it is fair to say that lithium salts have been used in patients without associated psychiatric illness, for example in the treatment of relapsing herpes simplex [75], HIV-associated neurocognitive impairment [76], and Alzheimer's [77], where the safety of the drug has been tested with good results. The proposed treatment would have relatively low doses (between 700-1000 mg/day), divided into two sub-doses and administered at lunch and dinner, with a progressive increase until reaching the maximum dose, and for a short period, depending on the patient's evolution, never exceeding 15 days. This scheme minimizes the risk of toxicity.

By September 21, 2021, over 228 million confirmed cases of COVID-19 have been reported worldwide, and over 4.6 million deaths, almost 60 000 reported in the last week (September 13-19) [78]. Lithium carbonate could be administered on a compassionate basis, especially in places where other treatments are not available. All risks should be understood prior to the administration and precautions taken under the supervision of a physician. Nevertheless, pre-clinical and clinical trials supporting the emergency use of lithium for COVID-19 should be planned and executed urgently. Taking all these into account, our group is currently working on obtaining pre-clinical evidence that permits the advancement to clinical trials.

Conclusions

Lithium salts represent a simple drug formulation, and their low production costs could make a difference in terms of access to effective drugs against COVID-19. As outlined, its antiviral and immunomodulatory effects can be useful in the treatment of COVID-19. It directly inhibits coronavirus replication and may also indirectly enhances antiviral responses of cytotoxic T-lymphocytes by downregulating the inhibitory receptor PD-1. Its immunomodulatory properties are a consequence of decreased production of IL-6 and IL1β and increasing production of IL-10. Therefore, its use could be of great relevance in the treatment of severe patients with immune deregulation, such as the cytokine storm observed in SARS-CoV-2 infection.

Ethical approval: Not applicable

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Conflict of Interest Statement

The authors declare no commercial or financial associations that could be construed as a potential conflict of interest.