Abstract. — Disruption of intracellular Ca²⁺ homeostasis plays an important role as an upstream pathology in Alzheimer’s disease (AD), and correction of Ca²⁺ dysregulation has been increasingly proposed as a target of future effective disease-modified drugs for treating AD. Calcium dysregulation is also an upstream pathology for the COVID-19 virus SARS-CoV-2 infection and replication, leading to host cell damage. Clinically available drugs that can inhibit the disturbed intracellular Ca²⁺ homeostasis have been repurposed to treat COVID-19 patients. This narrative review aims at exploring the underlying mechanism by which lithium, a first line drug for the treatment of bipolar disorder, inhibits Ca²⁺ dysregulation and associated downstream pathology in both AD and COVID-19. It is suggested that lithium can be repurposed to treat AD patients, especially those afflicted with COVID-19.

Key Words: Lithium, Mitochondria, Endosome, Calcium, Amyloid, Tau, SARS-CoV-2, Infection, Replication.

Introduction

Alzheimer’s disease (AD) is the 6th leading cause of death in the United States and the 5th leading cause of death among those age 65 and older, without disease-modifying treatment. In 2020, the costs of treating dementia in the United States were projected to be about $256.7 billion. Most (>95%) cases of AD are sporadic (SAD); while <5% cases are familial AD (FAD). FAD arises from genetic mutations in the amyloid β precursor protein (APP), and presenilin 1 and 2 (PSEN1 and PSEN2), resulting in increased amyloid β peptide (Aβ42) fragments which aggregate into soluble intracellular amyloid oligomers and/or insoluble extracellular plaques. Pathological tau phosphorylation results in the formation of neurofibrillary tangles. Although pathological markers are common in both FAD and SAD, the etiology of SAD and associated AD pathology, including synaptic and cognitive dysfunctions, is largely unknown, which impedes the development of new effective drugs for AD treatment. The apolipoprotein E4 (ApoE4) allele is considered a predominant risk factor for SAD among all other recognized risk factors. This tends to shift current research focus from amyloid pathologies to tau pathologies or to a combination of both amyloid and tau alongside other related downstream AD pathologies. In turn, the following strategies have been proposed to develop new effective drugs for the treatment of AD patients: 1) Targeting an upstream AD pathology that results in other multiple pathology pathways; 2) Utilizing a combination of drugs targeting different AD aberrant pathways, given the multifaceted etiology of AD; 3) The prevention or treatment of AD patients in the early stages of their disease, thanks to the improved techniques for the early diagnosis of AD.

Besides AD, the ongoing COVID-19 pandemic has resulted in over 364 million infection cases and over 5.63 million deaths worldwide (https://covid19.who.int/), impacting every aspect of our societies. The elderly, notably the demented population, is one of the groups most at risk of having severe COVID-19 symptoms. AD patients have greater than seven-times the risk of being infected with the COVID-19 virus, and more than a two-fold rate of mortality. Disruption of intracellular Ca²⁺ homeostasis is considered an upstream pathological pathway in not only AD, but also SARS-CoV-2 virus infection and replication in COVID-19. Specifically, aberrant elevation of Ca²⁺ concentrations in the cytosol and endosome as well as associated amyloid pathology in AD promote SARS-CoV-2 virus binding to host cells, subsequent infection, and RNA replication in host cells — a potential underlying mechanism which could increase COVID-19 severity in AD
patients. This narrative review addresses mechanisms underlying neuroprotection via lithium (the current first-line treatment for patients with bipolar disorder) against AD and, to a lesser extent, against COVID-19. We propose that lithium provides protection in both AD and COVID-19, at least in part, by restoring the disrupted intracellular Ca\(^{2+}\) homeostasis. Lithium is expected to inhibit both AD and COVID-19 pathologies and therefore may be utilized as a potential repurposed drug for the treatment of AD patients, especially those also infected with SARS-CoV-2.

**Lithium as a Potential Therapeutic Drug for AD by Correcting Upstream Ca\(^{2+}\) Dysregulation and Aberrant Signaling Pathways**

Changes of cytosolic Ca\(^{2+}\) concentrations ([Ca\(^{2+}\)]\(_{c}\)) regulate a variety of physiological functions, such as cell survival, cell death, cell division, neurogenesis, synaptogenesis and autophagy, among others\(^{26-29}\). As shown in Figure 1, pathological and prolonged elevation of [Ca\(^{2+}\)]\(_{c}\), mitochondrial Ca\(^{2+}\) concentrations ([Ca\(^{2+}\)]\(_{m}\)) due to Ca\(^{2+}\) influx via over-activation of NMDAR\(^{30-34}\), AMPAR\(^{35-38}\) and metabotropic GluRs (mGluRs)\(^{39-42}\) glutamate receptors in AD results in multiple AD-like pathologies including neurodegeneration\(^{43-46}\), impaired neurogenesis\(^{34,47,48}\), disrupted autophagy\(^{34,49-51}\), and excessive inflammation, etc.\(^{33,52-55}\). Additionally, the SAD high risk protein, ApoE4, pathologically aggravates over-activation of NMDAR and subsequent activation of L type voltage-dependent Ca\(^{2+}\) channel (L-VDCC)\(^{56,57}\). Further, L-VDCC is increased in the hippocampus of AD transgenic mice\(^{58}\), which can be modulated by amyloid β peptide\(^{59}\). The Ca\(^{2+}\) release from the endoplasmic reticulum (ER) via InsP\(_3\) receptors (InsP\(_3\)Rs) and/or ryanodine receptors (RyRs) is also pathologically increased in AD, due to the PSEN1 or PSEN2 mutation\(^{60-66}\). This Ca\(^{2+}\) dysregulation described above has been considered an upstream trigger for multiple AD pathologies, including activation of cyclin-dependent kinases 5 (CDK-5)\(^{67-70}\) and glycogen synthase kinase-3β (GSK-3β)\(^{71-74}\), tau hyperphosphorylation, and the spreading of tau pathology\(^{75,76}\), mitochondrial damage\(^{77,79}\), elevation of reactive oxygen species (ROS)\(^{80,81}\), and energy failure\(^{82,83}\) (Figure 1). These pathologies, especially when combined, result in the previously mentioned downstream AD pathologies, and eventually lead to synaptic/cognitive dysfunction\(^{41,84-87}\) (Figure 1). A drug that can inhibit upstream Ca\(^{2+}\) dysregulation\(^{15,78}\) and associated tau pathology\(^{14,88}\) is expected to be a good candidate for all above mentioned AD pathologies and to be an effective treatment of AD patients.

Lithium has long been a primary drug for treating bipolar disorder and has been shown to exhibit neuroprotective properties in various neurodegenerative diseases, including AD\(^{89,90}\), stroke\(^{95-98}\), Parkinson’s disease\(^{92-94}\), Huntington’s disease\(^{100-105}\), and brain trauma\(^{106,107}\). In preclinical models of AD, lithium treatment has been reported to inhibit multiple pathological features of AD, including amyloid\(^{108-110}\) and tau\(^{111,112}\) pathology, oxidative stress\(^{113}\), autophagy impairment\(^{95}\), as well as synapse and learning/memory deficits\(^{109,114}\). In some clinical investigations, lithium at moderate doses improves cognitive function and memory performance in AD patients\(^{115,116}\). Although inhibition of GSK-3β and CDK-5 is thought to be one of the primary mechanisms for inducing lithium’s neuroprotective efficacies\(^{117,118}\), the role of Ca\(^{2+}\) modulation in mediating lithium-induced neuroprotection has been under-explored. Increasing evidence suggests that lithium also inhibits the upstream pathologically elevated [Ca\(^{2+}\)]\(_{m}\) and associated tau hyperphosphorylation, as well as other downstream AD pathological pathways\(^{93,95,119,120}\). As shown in Figure 1, lithium inhibits toxic glutamate-induced over-activation of NMDARs, both alone and when this NMDAR over-activation is aggravated by the AD high risk protein ApoE4\(^{90,93}\). Lithium may inhibit NMDAR by inhibiting NMDA NR2B subunit tyrosine phosphorylation due to suppression of Src/Fyn tyrosine kinase\(^{19,121}\). Lithium also suppresses excessive Ca\(^{2+}\) release caused by over-activation of InsP\(_3\)R in AD conditions by downregulating an aberrant level of the InsP\(_3\)R agonist, insP\(_3\)\(^{122}\). Additionally, the aforementioned effects of lithium indirectly reduce Ca\(^{2+}\) release from the ER via RyRs through inhibiting Ca\(^{2+}\)-induced Ca\(^{2+}\) release (CICR)\(^{13,123}\). Moreover, lithium has also been demonstrated to increase the number and activity of the sarco/endoplasmic reticulum Ca\(^{2+}\) ATPase (SERCA) pump and to facilitate the Ca\(^{2+}\) uptake from the cytosol to ER lumen, thus ameliorating cell damage due to significant ER Ca\(^{2+}\) depletion and associated ER stress\(^{24}\).

In neurophysiological conditions, transfer of Ca\(^{2+}\) from the ER into mitochondria through InsP\(_3\)Rs/RyRs plays an important role in the generation of mitochondrial ATP as an energy source\(^{25,124}\). However, excessive transfer of Ca\(^{2+}\) from the ER into mitochondria, together with impaired electronic transfer chain (ETC) function
caused by hyperphosphorylated tau in AD will impair mitochondrial function in energy production\(^{127-129}\). Furthermore, overloading mitochondria with \(\text{Ca}^{2+}\) due to elevated \(\text{Ca}^{2+}\) concentration in cytosolic space \(([\text{Ca}^{2+}]_{\text{c}})\), especially those transferred from the ER via InsP\(_3\)R/RyRs, pathologically increases the generation of reactive oxygen species (ROS)\(^{130-133}\). Lithium can inhibit upstream abnormal \(\text{Ca}^{2+}\) influx from extracellular space by ameliorating dysfunctional changes of NMDARs\(^{93,119,134}\), AMPAR\(^{135}\), Kainite (KA) receptors\(^{136}\), mGluRs\(^{135,137}\), as well as excessive \(\text{Ca}^{2+}\) transfer from the ER into mitochondria via InsP\(_3\)R/RyRs\(^{122,138,139}\). Lithium also promotes \(\text{Ca}^{2+}\) uptake into the ER lumen by increasing the SERCA \(\text{Ca}^{2+}\) pump activity\(^{124}\) and ameliorating ER stress and associated cell damage in AD\(^{120}\). Considering the ability of lithium to ameliorate the above-mentioned AD pathologies, it may be prudent to repurpose lithium as an effective disease-modifying drug for AD treatment\(^{72,91,93}\).

Intracellular \(\text{Ca}^{2+}\) homeostasis plays critical roles in determining cell survival and death\(^{140-144}\). Both an aberrant elevation of \([\text{Ca}^{2+}]_{\text{c}}\)\(^{145,146}\) and \(\text{Ca}^{2+}\) concentration in mitochondria \(([\text{Ca}^{2+}]_{\text{m}})\)\(^{127,147}\), and the depletion of ER \(\text{Ca}^{2+}\)\(^{148,149}\) contribute to neuronal death. Overloading mitochondria with \(\text{Ca}^{2+}\) collapses the mitochondria membrane potential and releases cytochrome c into the cytosol\(^{142,150}\), leading to caspase activation and apoptotic cell death\(^{127,150-152}\). Neurodegeneration and brain atrophy are commonly seen in AD patients\(^{153,154}\), and are key mechanisms underlying synapse/cognitive dysfunction\(^{85,155}\). Maintenance of cytosolic, especially mitochondrial \(\text{Ca}^{2+}\) homeostasis also plays prominent roles in neurogenesis and synaptogenesis\(^{48,156-159}\). Mounting evidence suggests that adult neurogenesis and synaptogenesis in AD are significantly impaired due to \(\text{Ca}^{2+}\) dysregulation\(^{34,47,48,77,160,161}\). Thus, drugs that restore intracellular \(\text{Ca}^{2+}\) homeostasis have been demon-
strated to protect and/or promote neurogenesis/synaptogenesis in various AD models. These drugs eventually improve synapse and cognitive dysfunction by restoring and/or promoting neurogenesis/synaptogenesis. Through the correction of disrupted intracellular Ca²⁺ homeostasis, lithium is expected to inhibit neurodegeneration and impaired neurogenesis/synaptogenesis, or even to further promote neurogenesis/synaptogenesis.

Physiological autophagy plays a key role in maintaining protein homeostasis, especially via the removal of harmful proteins, such as β-amyloid and tau proteins or their aggregates. It is known that intracellular Ca²⁺ homeostasis, especially in the lysosome and mitochondria, helps to maintain normal autophagy. Ca²⁺ dysregulation in the cytosolic space, mitochondria and or lysosomes in AD contributes to impaired autophagy, leading to the accumulation of AD pathological proteins and a vicious cycle of Ca²⁺ dysregulation. This in turn ultimately results in cell and synapse damage as well as associated memory impairments. Lithium has been proposed to suppress impaired autophagy in AD by ameliorating the upstream Ca²⁺ dysregulation and therefore restoring neuronal, synaptic, and cognitive functions.

The over-expression of inflammation cytokines is likely involved in cell damage and synaptic dysfunction in AD. Intracellular Ca²⁺ homeostasis plays an important role in regulating levels of cytokine production and inflammation. On the other hand, some pathologically elevated cytokines further disrupt intracellular Ca²⁺ homeostasis, forming a vicious cycle. The upstream Ca²⁺ dysregulation contributes to the excessive production of toxic cytokines (TNF-α, II-1, II-6, etc.) and associated neuroinflammation, leading to neuronal and glial cell damages. As shown in Figure 1, lithium can suppress excessive inflammation in AD brains via normalizing upstream Ca²⁺ dysregulation, eventually resulting in improvement of synaptic function and cognitive performance.

**Potential Utility of Lithium in Treating COVID-19 Patients by Ameliorating the Upstream Pathology of Ca²⁺ Dysregulation**

COVID-19 is a systemic disease, involving multiple organ failures. Massive inflammation (cytokine storm) and cell damage or death in various organs likely contribute to COVID-19-related mortality. Although multiple mechanisms and pathways are likely involved in the infection, replication and host cell damage caused by the COVID-19 virus SARS-CoV-2, Ca²⁺ dysregulation has been proposed to be an integral upstream pathological event. Infection of host cells by SARS-CoV-2 requires initial binding of spike (S) protein to the angiotensin-converting enzyme 2 (ACE2) receptor on the plasma membrane and subsequent cleavage of S protein into S1 and S2 by the transmembrane proteases, serine 2 (TMPRSS2) and/or cathepsin L, S1 binds to ACE-2 which can be promoted by the amyloid protein, while S2 fuses with the plasma membrane and facilitates the endocytosis and invasion of the virus into the host cells (Figure 1). Activation of cathepsin L is dependent upon the elevation of [Ca²⁺], caused by Ca²⁺ influx from various glutamate receptor subtypes or voltage-dependent Ca²⁺ channels (VDCC), and pathologically increased Ca²⁺ release from the ER via InsP₃/RyRs. Activation of the L type Ca²⁺ channel facilitates the SARS-CoV-2 viral entry and spread in host cells. Endocytosis of the SARS-CoV-2 virus inside the endosome and cytosol also depends on high levels of Ca²⁺ in the endosome lumen, which originates from elevated [Ca²⁺] in the endosome lumen. Lithium treatment of a small group of COVID patients showed significant benefits including improvement of inflammatory activity and the immune response.
Conclusions

Aged people, especially those in nursing homes, are disproportionately affected by the COVID-19 pandemic\textsuperscript{220,221}. Currently, 45 million people in the world suffer from AD, and this number is expected to triple by 2050\textsuperscript{1,222,223}. Unfortunately, no disease-modifying drugs have been developed for effective treatment of AD. A drug that can inhibit the pathologies of both AD and COVID-19 is expected to benefit those AD patients infected, or at high risk of being infected with SARS-CoV-2 virus. As shown in Figure 1 and discussed above, lithium inhibits the upstream pathology Ca\textsuperscript{2+} dysregulation in both AD and COVID-19 via its ability to restore intracellular Ca\textsuperscript{2+} homeostasis and could have the potential to be repurposed to treat AD patients suffering with COVID-19. Further timely preclinical and clinical investigations of this possibility are warranted.

Authors’ Contributions
H.W. conceived the idea. HW, SA, RMV, GL, and DMC contributed to the manuscript preparation. All the authors reviewed and approved the final manuscript.

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Conflicts of Interest
The authors declare no conflicts of interest.

Disclaimer
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