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Lithium and Its Impact on Cognition

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Abstract

Research data found evidence that lithium improves some of cognitive domains. In this article we narratively review the literature in relation to lithium and its impact on cognition focusing on up to date research. The results of using lithium in neurodegenerative disorders are promising in the treatment of mild cognitive impairment and Alzheimer's disease.

Keywords: Lithium; Bipolar affective disorder; Cognition, Alzheimer's disease

Introduction

Lithium salts were used initially in the treatment of gout and by the late 1800 its effect on mood was recognised. In psychiatry, lithium is used for the treatment of acute mania, for the adjunctivetreatment of major depression and as a mood stabiliser for the prophylaxis of bipolar affective disorder [1]. Bipolar affective disorders are associated with changes in cognitive function that persists during euthymic phase. Impairments in executive function and verbal memory have been found in bipolar disorder. Xu et al., (2020) [2] found some evidence that lithium improves some of these cognitive domains. In this article we narratively review the literature in relation to lithium and its impact on cognition focusing on up to date research data.

Lithium in Mood Disorder and Cognition

Patients with Bipolar Disorder (BD) usually display cognitive deficits with aging. The effect of lithium on cognition in bipolar disorder patients was examined across cognitive domains of attention, psychomotor speed, processing speed, working memory, intellectual functioning, verbal memory, visual memory, and executive functioning [3]. The authors found that lithium has a distinct impact on psychomotor speed in patients with bipolar disorder but not on attention. Burdick et al., (2020) [4] found a significant neurocognitive improvement in the global cognitive index score, California Verbal Learning test delayed recall and Trail-making test part B. The study suggested that Lithium may be beneficial to neurocognitive functioning in patients with bipolar disorder.

Lithium response in bipolar disorder correlates with improved cell viability of patient derived cell lines. Lithium enhanced BCL2 apoptosis regulator and GSK3B expression in these cells indicating cellular phenotypes related to the disease (mitochondrial membrane potential, cell proliferation) in both neural precursor cells and lymphoblastoid cell lines [5].

Lithium and Neuroprotection

There is a growing consensus in the literature that Lithium salts may provide neuroprotection by targeting multiple processes in certain neurodegenerative disorders such as Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, Traumatic Brain Injury and Stroke. Neuroimaging techniques identified that long-term lithium treatment is associated with increased total grey matter [6], increased hippocampal volume [7] and decreased white matter microstructural abnormalities [8].

The neuroprotective effects of lithium stems from its effect on modulating several mechanisms involving neurotrophic response, autophagy, oxidative stress, inflammation, and mitochondrialfunction [9]. Lithium impact those intracellular responses by inhibition of glycogen synthase kinase-3beta (GSK-3β) and Inositol Monophosphatase (IMP).

Glycogen Synthase Kinase-3 (GSK-3) plays a critical role in cognitive dysfunction associated with Alzheimer's Disease (AD). Nguyen and colleagues (2018) [10] demonstrate that GSK-3 plays a direct role in the regulation of the oscillations in hippocampus and pre-limbic cortex, and highlight

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a potential mechanism by which GSK-3 may contribute to cognitive decline in disorders of cognitive dysfunction. Lithium has disparate effects on spatial memory and neural oscillatory activity in those areas.

Lithium inhibits GSK-3β activity directly by preventing the bindingof Mg^{2+} to the catalytic core of GSK-3β, and indirectly through inducing the phosphorylation of the serine-9 residue of GSK-3β, leading to conformational changes and inactivation, which is required for enzymatic activity [9].

Another relevant mechanism of action of lithium is the inhibition of Inositol Monophosphatase (IMP) and Inositol Polyphosphate-1 (IPP). Lithium directlyinhibits IMP and IPP activity by the competitive displacementof Mg^{2+} from the catalytic site of the enzyme [11]. Such inhibition prevents the reuptake of inositol, leading to depletion of intracellular levels and subsequent inhibition of the phosphoinositol cycle.

Forlenza et al. (2016) [12] found that the neuroprotective effects of lithium in preclinical models of neurodegeneration, its therapeutic benefits in cognitive function and reduced biomarkers in clinical trials of mild cognitively impaired amnestic and AD patients at lower lithium doses (300 μg daily)than those typically used for mood stabilization. Wilson et al. (2020) [13] reported that the novel micro-dose lithium formulation, NP03, has disease-modifying effects in the McGill-R-Thy1-APP transgenic rat model of AD-like amyloidosis at pre-plaque stages, before frank amyloid-β (Aβ) plaque deposition, during which Aβ is primarily intraneuronal. During the early Aβ post-plaque stage, the authors found that NP03 rescues functional deficits in object recognition, reduces loss of cholinergic boutons in the hippocampus, reduces levels of soluble and insoluble cortical Aβ42 and reduces hippocampal Aβ plaque number. In addition, NP03 reduces markers of neuro-inflammation and cellular oxidative stress. Together these results indicate that micro dose lithium NP03 is effective at later stages of amyloid pathology, after appearance of Aβ plaques.

Comparing the various forms of Lithium, Habib et al. (2019) [14] reported Lithium Salicylate Proline (LISPRO), Lithium Carbonate (LC), and lithium salicylate prevented spatial cognitive decline, as determined by Morris water maze and depression as determined by tail suspension test. In addition, LISPRO treatment was superior in preventing associative memory decline determined by contextual fear conditioning and reducing irritability determined by touch escape test in comparison with LC and LS. In conclusion, low-dose LISPRO, LC, and LS treatment prevent spatial cognitive decline and depression-like behaviour, while LISPRO prevented hippocampal-dependent associative memory decline and irritability in APPswe/PS1dE9 mice. Lithium chloride attenuated hypoglycaemia-induced cognitive function impairment in rats; and it was associated with Wnt signalling up-regulation and reduction of inflammatory response. Our results suggested that activating Wnt signalling pathways and inhibiting inflammatory response were the therapeutic potential to prevent hypoglycaemia-induced neurological damage [15].

Tau was described [16] in hyperphosphorylated form in the Neurofibrillary Tangles (NFT) observed in the brains of individuals with Alzheimer's Disease (AD). Activation of the peripheral innate immune system or exposure to stress can induce inflammatory cytokines such as Interleukin 1B (IL-1B), IL-6 and Tumour Necrosis Factor-α (TNF-α). The data from Tan et al. (2010) [17] data from splenectomised rat model suggest that Lithium Chloride restored tau hyperphosphorylation and the inflammatory factors to control levels. Lithium affects tau pathology through the GSK-3β signalling pathway. At a biological level, Lithium also affect stress and resilience in neurotrophic and neuroprotection by activation of plasticity pathways. Lithium tends to enhance cellular proliferation, differentiation, growth and regeneration [18]. Sarkar et al. (2005) [19] reported that lithium induced autophagy through the GSK-3β and due to the prevailing inhibition of inositol monophosphatase pathway. Lithium treatment also modulates calcium influx in the mitochondria and enhances the mitochondrial respiratory rate, and protects DNA against damage from oxidative stress [20].

Traumatic Brain Injury (TBI) is a risk factor for a group of neurodegenerative diseases termed tauopathies, which includes Alzheimer's disease and chronic traumatic encephalopathy. Tauopathies are pathologically related by the accumulation of hyperphosphorylated tau (P-tau) and increased Total tau (T-tau). Rubenstein et al. (2019) [21] observed a reversal of the abnormal behaviour and cognitive deficits in Lithium Chloride-treated rmCHI mice (compared to the untreated rmCHI mice) throughout the time course, these drug-treated effects were most pronounced up until 10 and 12 months where the abnormal behaviour and cognition deficits began to gradually increase. In addition, T-tau, but more predominantly P-tau, levels were significantly reduced in the cortex and plasma by Lithium chloriderose approaching the biomarker levels in sham and drug-treated sham mice throughout the study period. Pan et al. (2018) [22] suggest that the cognitive benefits and brain Aβ42 lowering effects of Lithium Chloride are associated with enhanced brain clearance of Aβ42, possibly *via* brain microvascular transporter low density Lipoprotein Receptor-related Protein 1 (LRP1) upregulation and increased Cerebrospinal Fluid (CSF) bulk-flow, identifying a novel mechanism of protection by Lithium Chloride for the treatment of AD.

Lithium neuroprotection against Methamphetamine (METH)-induced neurodegeneration in the hippocampus may be *via* protein kinase B/GSK3β and cAMP Response Element Binding (CREB)/BDNF signalling pathways [23]. In this study lithium attenuated METH-stimulated apoptosis, oxidative stress, and inflammation; while improving the extent of BDNF and P-CREB.

Another important neuroprotective effect of lithium is thestimulation of synthesis and release of neurotrophic factors. Increased availability of Brain-Derived Neurotrophic Factor (BDNF) and Vascular Endothelial Growth Factor (VEGF) protects neurons against neurotoxicinsults, stimulates hippocampal neurogenesis, increases synapticplasticity and Long-Term Potentiation (LTP), and positively regulates cell survival [24]. In addition, brain lithium levels were associated with increased N-acetyl aspartate levels suggesting neuroprotective and neurotrophic effects of lithium treatment [25].

Furthermore, Priebe and Kanzawa (2020) [26] demonstrated reduced progression of Alzheimer's pathology with micro-dose lithium in those with trisomy 21. The authors suggest that lithium confers a clinically significant benefit in AD by impeding accumulation of the aberrant proteins central to the putative pathogenesis.

Lithium and Other Disorders

Loss of gray matter after stroke has been associated with cognitive impairment. Lithium Carbonate was tried in a post-stroke population [27]. There was a significant interaction between higher lithium dose and increased global gray matter volume and a correlation between

higher lithium dose and improved verbal memory. The authors advocated Lithium pharmacotherapy in stroke patients may provide a rationale for future trials assessing therapeutic potential of lithium in a post-stroke population. Liu et al. (2018) [28] showed lithium chloride inhibited glycogen synthase kinase-3β activation, which on one hand, suppressed downstream CRMP-2/NR2B, thus diminishing the excitotoxicity index level; and on the other, stabilized β-catenin, thus modulating its downstream apoptosis-related factors such as NF-κB, Bcl-2 and Bax. Meanwhile, glycogen synthase kinase-3β inactivation was paralleled by decreased neuronal death, improved neurological functional deficits and ameliorated cognitive deficits in intracerebral haemorrhage animals. These findings indicate that lithium chloride improves glutamate-mediated excitotoxicity-induced cognitive deficits after intracerebral haemorrhage and that lithium chloride might be a potential therapeutic agent for brain damages caused by intracerebral haemorrhage.

Cranial radiotherapy treatments can harness hippocampal neurogenesis in childhood cancer survivors. Lithium treatment was propose as intermittent therapy in childhood cancer survivors in order to first make neural progenitors proliferate and then, upon discontinuation, allow them to differentiate [29]. Lithium treatment reverses irradiation-induced loss of hippocampal neurogenesis and cognitive impairment even when introduced long after the injury. Also, the treatment ameliorated deficits in spatial learning and memory retention observed in irradiated mice.

Prophylactic lithium also alleviates postoperative cognition impairment by phosphorylating hippocampal glycogen synthase kinase-3β (Ser9) in aged rats [30]. The changes in the hippocampal glycogen synthase kinase-3β (p-GSK-3β) phosphorylation at serine 9, interleukin-1β (IL-1β) expression, and PI3K cascades displayed corresponding changes that were parallel to the alterations of spatial memory, and inhibition of PI3K and GSK-3β suggested upstream PI3K activation leads to downstream change in p-GSK-3β and IL-1β. Postoperative cognitive dysfunction is a common complication in elderly patients after surgeries involving anaesthesia. Wang et al. (2020) [31] examined the effects of lithium chloride on Sevoflurane (SEV) anaesthesia-induced cognitive dysfunction and neuron apoptosis in rats. Anaesthesia with SEV significantly impaired memory performance, induced oxidative stress and hippocampal neuron apoptosis, and stimulated GSK-3β activity. Treatment with lithium chloride ameliorated SEV-induced cognitive disorder in rats by inhibiting the GSK-3β/β-catenin signalling pathway. In addition, lithium chloride reduced hippocampal neuron apoptosis and oxidative stress induced by SEV anaesthesia. These results suggest that lithium chloride may have potential for development into a therapeutic agent for treatment of SEV anaesthesia-induced cognitive dysfunction.

The effects of lithium are significant in Amyotrophic Lateral Sclerosis (ALS) patients carrying genetic variations in the UNC13 presynaptic protein, which occur in ALS/frontotemporal dementia and psychiatric disorders such as bipolar disorder [32]. Chiò et al. (2013) [33] conducted a multicentre, double-blind, placebo-controlled trial of lithium versus placeboin ALS. Unfortunately, the study results did not support any evidence of increased survival associated with lithium treatment. On the other hand, Busceti et al. (2008) [34] suggested that the neurotrophic response and synaptogenesis induced by lithium could be relevant for the treatment of ALS, with apossible impact on disease progression.

Lithium enhances myoblast fusion and myogenic differentiation which has implications for the treatment of several cognitive and myopathic conditions [35]. Moreover, lithium protects retinal neurocytes following nutrient deprivation or partial nerve crush from ischemia-induced damage and enhances light response in rat retina following ischemia–reperfusion injury [36].

Lithium has been also studied in Parkinson's and Huntington's disease but the results are not consistent.

Conclusion

Literature data from experimental, and clinical studies have pointed to neuroprotection and possible anti-dementia effect of lithium. The results of using lithium in neurodegenerative disorders are promising in the treatment of mild cognitive impairment and Alzheimer's disease.

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