

Lithium and neuroprotection: translational evidence and implications for the treatment of neuropsychiatric disorders

Diniz BS, Machado-Vieira R, Forlenza OV: Neuropsychiatr Dis Treat. 2013;9:493-500. doi: 10.2147/NDT.S33086. Epub 2013 Apr 12.

Source: Department of Mental Health, National Institute of Science and Technology - Molecular Medicine, Federal University of Minas Gerais, Belo Horizonte, Brazil.

Abstract

In the last two decades, a growing body of evidence has shown that lithium has several neuroprotective effects. Several neurobiological mechanisms have been proposed to underlie these clinical effects. Evidence from preclinical studies suggests that neuroprotection induced by lithium is mainly related to its potent inhibition of the enzyme glycogen synthase kinase-3 β (GSK-3 β) and its downstream effects, ie, reduction of both tau protein phosphorylation and amyloid- β 42 production. Additional neuroprotective effects include increased neurotrophic support, reduced proinflammatory status, and decreased oxidative stress. More recently, neuroimaging studies in humans have demonstrated that chronic use is associated with cortical thickening, higher volume of the hippocampus and amygdala, and neuronal viability in bipolar patients on lithium treatment. In line with this evidence, observational and case registry studies have shown that chronic lithium intake is associated with a reduced risk of Alzheimer's disease in subjects with bipolar disorder. Evidence from recent clinical trials in patients with mild cognitive impairment suggests that chronic lithium treatment at subtherapeutic doses can reduce cerebral spinal fluid phosphorylated tau protein. Overall, convergent lines of evidence point to the potential of lithium as an agent with disease modifying properties in Alzheimer's disease. However, additional long-term studies are necessary to confirm its efficacy and safety for these patients, particularly as chronic intake is necessary to achieve the best therapeutic results.

Lithium's gene expression profile, relevance to neuroprotection. A cDNA microarray study

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Source: Department of Internal Medicine B, Ziv Medical Center, Safed, Israel. Abstract

Lithium can prevent 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) dopaminergic neurotoxicity in mice. This is attributed to induced antioxidant and antiapoptotic state, which among other factors results from induction of Bcl-2 and reduction of Bax, however, cDNA microarray reveals that this represents only one cascade of lithium targets. From analyzing the gene expression profile of lithium, we are able to point out candidate genes that might be involved in the antioxidant and neuroprotective properties of lithium.

Among these are, the cAMP response element binding (CREB) protein, extracellular signal-regulated kinase (ERK), both CREB and ERK-part of the mitogen-activated kinase pathway-were upregulated by lithium, downregulated by MPTP, and maintained in mice fed with lithium chloride (LiCl) supplemented diet and treated with MPTP. Our positive control included tyrosine hydroxylase which both its mRNA and protein levels were independently measured, in addition to Bcl-2 protein levels. Other important genes which were similarly regulated are plasma glutathione peroxidase precursor (GSHPX-P), protein kinase C alpha type, insulin-like growth factor binding protein 4 precursor, and interferon regulatory factor. In addition, some genes were oppositely regulated, i.e., downregulated by lithium, upregulated by MPTP, and maintained in mice fed with LiCl supplemented diet and treated with MPTP, among these genes were basic fibroblast growth factor receptor 1 precursor, inhibin alpha subunit, glutamate receptor subunit zeta 1 precursor (NMD-R1), postsynaptic density protein-95 which together with NMD-R1 can form an apoptotic promoting complex. The discussed targets represent part of genes altered by chronic lithium. In fact lithium affected the expressions of more than 50 genes among these were basic transcription factors, transcription activators, cell signaling proteins, cell adhesion proteins, oncogenes and tumor suppressors, intracellular transducers, survival and death genes, and cyclins, here we discuss the relevance of these changes to lithium's reported neuroprotective properties.