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[Crit Rev Neurobiol.](#) 2004;16(1-2):83-90.

Neuroprotective and neurotrophic actions of the mood stabilizer lithium: can it be used to treat neurodegenerative diseases?

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Abstract

The mood stabilizing drug lithium has emerged as a robust neuroprotective agent in preventing apoptosis of neurons. Long-term treatment with lithium effectively protects primary cultures of rat brain neurons from glutamate-induced, NMDA receptor-mediated excitotoxicity. This neuroprotection is accompanied by an inhibition of NMDA-receptor-mediated calcium influx, upregulation of anti-apoptotic Bcl-2, downregulation of pro-apoptotic p53 and Bax, and activation of cell survival factors. Lithium treatment antagonizes glutamate-induced activation of c-Jun-N-terminal kinase (JNK), p38 kinase, and AP-1 binding, which has a major role in cytotoxicity, and suppresses glutamate-induced loss of phosphorylated cAMP responsive element binding protein (CREB). Lithium also induces the expression of brain-derived neurotrophic factor (BDNF) and subsequent activation TrkB, the receptor for BDNF, in cortical neurons. The activation of BDNF/TrkB signaling is essential for the neuroprotective effects of this drug. In addition, lithium stimulates the proliferation of neuroblasts in primary cultures of CNS neurons. Lithium also shows neuroprotective effects in rodent models of diseases. In a rat model of stroke, post-insult treatment with lithium or valproate, another mood stabilizer, at therapeutic doses markedly reduces brain infarction and neurological deficits. This neuroprotection is associated with suppression of caspase-3 activation and induction of chaperone proteins such as heat shock protein 70. In a rat model of Huntington's disease (HD) in which an excitotoxin is unilaterally infused into the striatum, both long- and short-term pretreatment with lithium reduces DNA damage, caspase-3 activation, and loss of striatal neurons. This neuroprotection is associated with upregulation of Bcl-2. Lithium also induces cell proliferation near the injury site with a concomitant loss of proliferating cells in the subventricular zone. Some of these proliferating cells display neuronal or astroglial phenotypes. These results corroborate our findings obtained in primary neuronal cultures. The neuroprotective and neurotrophic actions of lithium have profound clinical implications. In addition to its present use in bipolar patients, lithium could be used to treat acute brain injuries such as stroke and chronic progressive neurodegenerative diseases.

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