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Review Article

The Role of Lithium Chloride in Nutrition and Stem Cell Growth Kinetics: A Review

Mahin Homayoun[1], Davood Mehrabani[2,3,4,5*], Mohammad Amin Edalatmanesh[1], Mehrdad Shariati[6]

1. Department of Molecular Biology, Shiraz Branch, Islamic Azad University, Shiraz, Iran
2. Stem Cell Technology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
3. Burn and Wound Healing Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
4. Comparative and Experimental Medicine Center, Shiraz University of Medical Sciences, Shiraz, Iran
5. Li Ka Shing Center for Health Research and Innovation, University of Alberta, Edmonton, AB, Canada
6. Department of Biology, Kazeroon Branch, Islamic Azad University, Kazeroon, Iran

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**Corresponding author:*
Davood Mehrabani, PhD;
Stem Cell Technology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.
Tel: +98-71-32341025
Email: mehrabad@sums.ac.ir

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ABSTRACT

Lithium chloride (LiCl) is an essential trace element and the smallest alkali metal with an atomic weight of 6.9 that is found in grains, vegetables and in supplemented drinking water sources that seems to have profound effects on human well-being, susceptibility to several diseases and stem cell growth kinetics. Much remains to be learned and understood about the implications of LiCl in nutrition and stem cell culture. This review is going to consider what is known about the nature of this competition and the knowledge towards understanding of lithium biology and its application in medicine in osteomyopathology, immunity, neuroprotectionm, radio- and chemotherapy, cancer and proliferation of stem cells.

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INTRODUCTION

Lithium chloride (LiCl) is an essential trace element and the smallest alkali metal with an atomic weight of 6.9 that is found in grains, vegetables and in supplemented drinking water sources (1). It has neuroprotective activity to be used as a mood stabilizer in treatment of bipolar disorders and manic depressive illness with approval from Food and Drug Administration (2). LiCl has been used in treatment of CNS injuries and degenerative diseases such as spinal cord injury (SCI), stroke, Alzheimer's disease, Parkinson's disease, Huntington's disease, and in epilepsy (2-5). In trace levels, it may to some extent prevent dementia (6), suicide (7), and homicide (8).

Totally, three major hypotheses were reported regarding the mechanisms of action and its therapeutic activity in degenerative diseases including (i) Cyclic AMP (9), (ii) Inositol depletion (10), and (iii) Inhibition of protein kinases, such as glycogen synthase kinase (GSK), with subsequent activation of the Wnt neurodevelopmental pathway (11). In addition, it increases the anti-apoptotic protein Bcl2 levels in the frontal cortex of brain (12). It has been used as an anticancer drug in combination with radiotherapy (13) and in treatment of granulocytopenia caused by radiation and chemotherapy (2).

Its protective effect against cadmium toxicity was previously investigated (14). LiCl can also attenuate lead induced toxicity confirmed by use of mouse non-adherent bone marrow cells and has been introduced a potentially new therapeutic strategy and a cost-effective approach to minimize destructive effects of lead toxicity on bone marrow derived stem cells (BMSCs) (15). LiCl can play an important role in boosting immunoglobulins after vaccination, and in enhancing of natural killer activity (2). Lee *et al.* displayed that LiCl can stimulate lipid accumulation in hepatocytes and macrophages via an increase in PKA-dependent reactive oxygen species (ROS). ROS are important signaling molecules regulating diverse physiological and pathological processes, such as cell proliferation, differentiation, migration and death, in almost all tissues (16).

An increase in body weight can happen after LiCl administration in human patients (17) and experimental rats (18), because LiCl can stimulate glucose uptake and glycogen production by mimicking insulin action in isolated adipocytes (19) and shows insulin-like effects in rat hepatocytes by promoting synthesis of glycogen from glucose (20). In these conditions, LiCl was demonstrated to have a protective role against oxidative stress caused by serum deprivation (21). This review is going to consider the knowledge towards understanding of lithium biology and its application in osteomyopathology, immunity, neuroprotectionm, radio- and chemotherapy, cancer and proliferation of stem cells.

LiCl in Osteomyopathology

Findlay *et al.* showed the therapeutic role of LiCl in correction of weakness and myopathology in a preclinical model of limb girdle muscular dystrophy 1D (LGMD1D) via GSK3β inhibition (22). LiCl was shown to enhance osteogenesis in wear particle-induced osteolysis via GSK-3β signaling pathway inhibition and to attenuate osteoclastogenesis via suppressing the nuclear factor-kappa B (NF-κB) pathway (23-25).

LiCl Role in Immunity

Several studies have illustrated that LiCl can regulate some biological processes, such as inflammation, apoptosis, and glycogen synthesis (23, 24, 26). In addition to these biological processes, the role of LiCl in regulating inflammation in various immune cell models, especially macrophages, in the context of inflammatory diseases, have been investigated (27-29). LiCl has been used in the clinical treatment of various conditions such as boosting immunoglobulins after vaccination, and enhancing natural killer activity (1). LiCl has a protective role against oxidative stress caused by serum deprivation (21). Yang *et al.* showed the immunomodulatory effects of LiCl to alleviate Ti nanoparticle-mediated inflammatory reactions by driving macrophage polarization and recommended LiCl as an effective therapeutic alternative for preventing and treating wear debris-induced inflammatory osteolysis (30).

LiCl Effect on Stem Cells

Stem cells are a promising tool to improve tissue repair, or to regenerate damaged tissues for regenerative medicine purposes, because they can differentiate into other cell lineages (31). As stem cells have a great role in regenerative medicine (32), addition of nutrients in cell culture media can influence the number and the time that cells can reach confluency for further expansion (33). However following cell transplantation, these cells can rapidly disappear and apoptosis happens in the affected area due to serum deprivation, low survival in the affected area (34), and activation of autophagy to protect the cells (34, 35). In these conditions, LiCl was demonstrated to have a protective role against oxidative stress caused by serum deprivation (21). It increases stem cell proliferation and modulates stem cell differentiation through GSK-3beta-dependent beta-catenin/Wnt pathway activation (36-38).

Several researchers illustrated that LiCl can attenuate adipogenesis, and enhance osteogenic differentiation in BMSCs (30, 37, 39). Yu *et al.* demonstrated that LiCl reduces abnormal adipogenic activity and simultaneously increases the osteogenic differentiation of femoral head of BMSCs by activating the β-catenin pathway (37). Li *et al.* in a 3D printed PCL-PDA-LiCl scaffolds depicted a promotion in chondrogenesis and concluded LiCl to be a potential candidate for future cartilage tissue engineering (40).

The modulating effect of LiCl on proliferation of hematopoietic stem cells was previously shown (41). It can enhance the efficiency of induced pluripotent stem cell-derived neurospheres (42). The effect of LiCl on cell proliferation and osteogenic differentiation of stem cells from human exfoliated deciduous teeth was reported (43). It can promote the odontoblast differentiation of hair follicle neural crest cells by activating Wnt/β-catenin signaling (44). It can alleviate the root resorption and cementum impairment due to orthodontic forces by cementoblast differentiation activity via Wnt/β-catenin signaling (45-47). LiCl can promote myogenic differentiation and myoblast fusion in muscle cells which has a central role in treatment of several myopathic diseases (48).

LiCl can also attenuate lead induced toxicity confirmed by use of mouse non-adherent bone marrow cells and has been introduced a potentially new therapeutic strategy and a cost-effective approach to minimize destructive effects of lead toxicity on bone marrow derived stem cells (BMSCs) (15). Lee *et al.* displayed that LiCl can stimulate lipid accumulation in hepatocytes and macrophages via an increase in PKA-dependent reactive oxygen species (ROS). ROS are important signaling molecules regulating diverse physiological and pathological processes, such as cell proliferation, differentiation, migration and death, in almost all tissues (16).

Neuroprotective Effects of LiCl

The neural stem cells (NSCs) are multipotent cells with proliferation and differentiation capacity for neurons, astrocytes, and oligodendrocytes playing a key role in the repair of damaged brain tissues and the treatment of neurodegenerative diseases (49). As NSCs are a powerful resource for cell-based transplantation therapies, it is of great importance to find targets that regulate the proliferation and differentiation of these cells (50). LiCl was shown to have a vital role in proliferation of neural stem cells, neuronal plasticity and survival, neural differentiation, production of brain-derived neurotrophic factor (BDNF) and decreasing DNA damage (γH2AX) and apoptosis (51).

LiCl was found to have neuroprotective effect against excitotoxic lesions and improves the CNS neurogenesis, inhibits apoptosis, and protects brain tissue in ischemic and traumatic injuries (52-54) and also protects against β-amyloid induced cell death (55). Its anti-apoptotic effects are by inducing up-regulation of B-cell lymphoma protein-2 (bcl-2) as well as suppressing the calcium-dependent activation of pro-apoptotic signaling pathways (56). LiCl identical to antidepressants can increase hippocampal neurogenesis (57). The beneficial effect of LiCl was validated for motor function as well as improvement in learning and memory together with an increase in dendrite spine density in Parkinson's disease models through Rotarod test and Morris water maze analysis. LiCl treatment could enhance the proliferation in NSCs and promote the dopaminergic neuronal differentiation (58). These effects are undertaken via N-methyl-D-aspartate receptors (NMDA-R) as well as nitric oxide and Wnt pathways and inhibition of inositol monophosphatase enzyme (59-63).

Zhang *et al.* presented the beneficial effects of LiCl in promoting the proliferation abilities of NSCs and preventing the cells from differentiating by activation of the Wnt signaling pathway (64). Soleimani and Ghasemi found that that LiCl was able to facilitate dopaminergic differentiation of human immortalized RenVm cells by affecting Wnt-frizzled signaling pathway (65). Wnt signaling pathway has been shown to have a key role in controlling neurogenesis, and differentiation of NSCs, and leads to accumulation of β-catenin in the cytoplasm. Wnt signaling pathway is antagonized by GSK-3β, and has an important role in regulation of several developmental processes, such as cell proliferation, apoptosis, migration, polarity, and fate decisions and development of central nervous system (CNS) (66).

Mohammadshirazi *et al.* revealed that combinational therapy of NSCs with LiCl and LiCl individually were adequate to ameliorate more than partial functional recovery and endogenous repair in spinal cord injury (SCI) of rats (4). Abdanipour *et al.* suggest that LiCl can protect neural cells and effectively enhance locomotor function in rats with SCI (3). Olson demonstrated combining treatments can develop the improvement in decreasing the difficulties caused by SCI (67). This neuroprotective effect in enhancing locomotor function is through up-regulation of endogenous brain-derived neurotrophic factor (BDNF) (68, 69) and vascular endothelial growth factor (70).

Zhang *et al.* have mentioned to the therapeutic potential of LiCl in cell replacement strategies in central nervous system injuries due to its ability to promote survival and neuronal generation of grafted NSCs and a reduction in host immune reaction (71). Yuan *et al.* exhibited that a combination of endogenous neural stem cell mobilization using granulocyte-colony stimulating factor (G-CSF) and LiCl treatment can lead to highly reduced incidence of hydrocephalus after intraventricular hemorrhage (IVH), by inhibiting neuronal apoptosis (72).

LiCl in Radio- and Chemotherapy Complications

LiCl has been used in the clinical treatment of various conditions such as treating granulocytopenia due to radiation and chemotherapy (2). Zanni *et al.* showed that LiCl increases proliferation of hippocampal neural stem/progenitor cells and rescues irradiation-induced cell cycle arrest *in vitro*. They demonstrated that LiCl is a very promising candidate to protect juvenile brain from radiotherapy and to improve the quality of life for those children who survive their cancer (63). LiCl has a great potential for rescuing neurogenesis in the adult and juvenile brain after irradiation (73, 74). LiCl can be a promising medication in treatment of radiotherapy-induced neurocognitive decline with a great potential to rescue neurogenesis in the adult and juvenile brain after irradiation (73, 74).

Anticancer Effects of LiCl

LiCl as a newly discovered antineoplastic and cytotoxic promising agent in new combination treatments is considered as an inhibitor of the inositol monophosphatase (IMPase), glycogen synthase kinase 3β (GSK 3β) pathway (an agonist known to activate the Wnt/β catenin signaling), the phosphoinositide signaling pathway and adenylate cyclase (36, 75-77). GSK-3β, and serine-threonine protein kinase are involved in cell proliferation, differentiation, survival, apoptosis, and tumorogenesis. LiCl was shown to be a tumor suppressor for certain types of tumors, but it may promote cell growth and development in other tumor types (78). LiCl has biphasic effect by inhibition or stimulation of the growth of normal and cancer cells. Its function as a specific radio-sensitizer for tumor cells makes it to be widely used in combination therapy as anticancer drug opening a therapeutic window in combination with radiotherapy (13). Several researchers have illustrated that tumor cells proliferation was significantly inhibited by LiCl in a dose- and time-dependent manner, compared with control cells (75, 79). Erguven *et al.* reported concentration-dependent effects of LiCl on prostate cancer stem cells through growth factor midkine (MK) (80).

Conclusion

Lithium Chloride (LiCl) was demonstrated to have profound effects on human well-being, susceptibility to several diseases such as mood disorders, neurodegenerative disease, and cancer and stem cell growth kinetics. Much still needed to be learned and understood about the implications of LiCl in clinical nutrition and medicine. This review considered what is known about the nature of this competition and the knowledge towards understanding of lithium biology and its application in medicine in osteomyopathology, immunity, neuroprotectionm, radio- and chemotherapy, cancer and proliferation of stem cells.

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Conflict of Interest

None declared.

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