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Review Article

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Lithium: Immunomodulatory and Anti-Infectious Activities

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Abstract

Lithium (Li), a well-known immunomodulatory agent, has been in use for the treatment of several infectious diseases. Li mainly acts through GSK3β inactivation and several other signalling pathways, which are directly involved in the activation of innate immune system. Li therapy has been shown to cause effective modulation of various inflammatory cytokines, and has also been shown to boost immunity in several disease models. Apart from treatment for mania, Li has also been proved to be effective against infections caused by viruses, bacteria, parasites, and certain life-style disorders. Its effects, ranging from common defensive capabilities to complex pathways for protection of human body, make Li extraordinary. Thus, Li is an absolute requirement that can be a solution for some of the immune related disorders. This review mainly focuses on pharmacology, immune reactions of different cell types, and anti-infectious activities of Li.

Keywords: Cytokines, Immunomodulation, Infectious diseases, Lithium

Introduction

Li, the third lightest inorganic element discovered by August Arfwedson in 1817 in Sweden was first named as "Lithion" by Berzelius. As Li is not a common constituent in the body, it is very difficult to estimate its concentration by normal spectroscopy but can be determined by atomic absorption and flame emission spectroscopy [1]. It is found in most of the animal tissues like endocrine glands, muscles and bone, differing in amount individually, and is also found in drinking water [2]. Due to the widespread presence of Li, Sir Garrod AB felt it be an essential mineral element, and he observed that Li compounds may be used for gout and rheumatic cases [3]. Later, it has been used as a promising therapy for mania, and still a lot of research is being carried out for its effects in many neuroprotective, metabolic and infectious diseases, despite its own toxicities. As Li acts on various molecular targets and is involved in immune function, directly, there can be a large possibility of therapeutic advance in wide areas of diseases. Modulatory effects of Li on cytokines, HPA axis and inflammation are also well known [4]. It inhibits the prostaglandin synthesis and exerts antiviral and antidepressive properties. Li is helpful in haematological disorders by enhancing the lymphocyte proliferation and platelet aggregation. Cell-mediated and humoral mediated immunodeficiency was reversed by Li by restoring the helper cell production, and can be used as an immunologic adjuvant [5, 6]. It also supported TNF-prompted apoptosis by increasing caspase-3 activity and also induced autophagy by inhibiting inositol mono phosphatase by depleting IP3 levels and mTOR activation, which ultimately leads to the GSK3 inhibition [7, 8].

Pharmacology

Li competes with cations (Na^+, K^+, Mg^{+2}& Ca^{+2}) and ammonia groups [9]. Li does not bind to plasma proteins but can be completely absorbed through gastrointestinal tract, and its peak serum concentrations reaches by 3 h and plasma half-life in the normal adult humansis 20-27 h but in rats, it is 3.5 h and can be easily excreted by kidneys [10]. It mainly acts on numerous Mg^{+2} -stimulated and dependent enzymes and also such as GSK3, phosphomonoesterases, IMPase, Adenylyl cyclase, pyruvate kinase and many others by replacing the bound Mg^{+2} for association with enzymes but not all enzymes are inhibited remarkably. Apart from that, Li can also interact with calcium-dependent enzymes and there can be several potential targets for it to act upon different enzymes and metal ion catalytic processes [11]. Thus, it is involved in regulating several signal transduction and metabolic pathways by direct involvement in glycogen synthesis, depletion of inositol, apoptosis and blocking ligand signalling through calcium which effects metabolism, cell proliferation, and neuro protection [12]. Li is transported out by sodium transporter system and has an indirect effect on potassium and chloride transport system [13]. It can cross through placental membrane also and is capable of having a teratogenic effect. Li can be effluxed bidirectional in erythrocytes by Na^+ - K^+ ATPase and co-transport, sodium-Li and anion exchange and leak pathways [1]. Accumulation of diacylglycerol and inositol levels leads to the prolonged activation of protein kinases and attenuation of brain response to stimuli, respectively. Adrenergic and cholinergic predominance can be decreased by Li's well-known functions of competing with bound Mg^{+2} which ultimately affect the GTP binding

in G-protein-coupled receptors activated signal transduction pathway, and this balancing of adrenergic and cholinergic mechanisms is helpful in a large number of pathological conditions. Li-induced GSK deficiency exerts anti-inflammation function by reducing the pro-inflammatory cytokines secreted by TLR stimulated monocytes and also regulation of anti-inflammation, this GSK3 inhibitory activity of Li is capable of balancing pro-inflammatory and anti-inflammatory cytokines and can be useful for many inflammatory disorders both centrally and peripherally, as it can cross CNS. Li also regulates cytokine production by acting upon the immune cells like natural killer cells, macrophages and dendritic cells [14]. Enhancement of B-lymphocytes and T-lymphocytes synthesis and increase in phagocytic activity of macrophages made Li a helpful feature in many pathological conditions [9]. Li also stimulates the release of serotonin, and inhibits norepinephrine and dopamine release. It is well known for its immunopotentiating activity as it opposes eicosanoid by inhibiting prostaglandin E1 synthesis and decreases the turnover of arachidonic acid in phospholipids that eventually slow down immunity [15].

GSK3-mediated immunomodulation

Li is an uncompetitive inhibitor of GSK3 which decreases the dephosphorylation of protein kinases by AKT activation and prevents apoptosis by inhibiting the serine-threonine phosphatase activity and produces many biochemical effects [16]. It can antagonise the dopamine-mediated circadian rhythm regulated gene expression/behaviour in rodents by interfering in AKT: βArr2: PPA2 signalling complex and controlling the GSK3 signalling by D2 receptors [17]. GSK3 interacts with protein kinase family and is involved in a variety of cellular functions and dysfunction of GSK-3 can lead to many pathological conditions. Decreased parasite burden in parasitic infections like leishmania and trypanosome are suggested via GSK3 inhibition in in vivo experiments. Recently LiCl showed dramatical inhibition of Plasmodium berghei multiplication in vivo, similar to, chloroquine by enhanced phosphorylation of GSK3 in liver. PfGSK3 gene has been recognised in P. falciparum, expressed in trophozoite stages but due to complex nature of the active binding site, there is difficulty in designing inhibitors [18]. Inhibition of GSK3 disrupts the Wnt signalling protein complex and cell fates during embryonic development. Li, as GSK3 inhibitor, is able to increase glycogen formation and decrease the glucose turn-out in liver and it is already known that it can also hamper non-kinase targets (inositol monophosphatase and histone deacetylase) by which all these factors may be helpful in treating diabetes. With reference to Sun et al., it is confirmed that LiCl (5 mM) is able to reduce secreted Aβ aggregates in APP-C99 expressed COS-7 cells, and the same is confirmed in Chinese hamster ovary cells and in HEK cells at half-MIC of Li (1-2 mM). Whereas, in vivo it is noticed to reduce phosphorylation of tau and decreased filament burden and Aβ levels by 40–50% when the serum absorption rate of Li was in therapeutic range [19]. Li possessing GSK3 inhibitor property is now proved as an anti-inflammatory agent showed increased survival rate by producing cytokine balance, thereby, decreasing the disease burden in a variety of bacterial infections like Klebsiella pneumonia, Francisella tularensis, Streptococcus pyogenes, and Burkholderia pseudomallei, in various degrees [20].

Non-specific enzyme-mediated immunomodulation

Two enzymes IMPase and IPPase involved in phosphoinositol signalling pathway denovo synthesis can be inhibited by Li at 0.8 mM, noncompetitively [21]. Enzymes of IPPase are involved in recycling of IP3 to inositol to maintain PI-mediated signalling [22], and are likely to affect autophagy, apoptosis, cell growth and mood stability via reducing the accumulation of aggregate-prone proteins like A53T and A30P mutants of synuclein in PC12, Huntington. As Li has a property of crossing the blood brain barrier, central nervous disorders like mania, depression can be easily treated [23]. Depleted inositol levels produce biochemical and behavioural changes. There is also a controversy that upon chronic administration of Li therapy (0.2% for 4 weeks, having serum concentrations of 0.6–0.8 mM) observed increased activity of IMPase-1 in the hippocampus and cerebral cortex samples [24]. Li also interacts with fructose 1, 6-bisphosphatase, bisphosphate nucleotidase, phosphoglucomutase (PGM), valproate inhibitable enzymes, cAMP, arachidonic acid, adenylate cyclase and neurotrophic pathways. Inhibition of FBPase is under the trails for the treatment of diabetes. Inhibition of BPNase/PAP phosphatase acts as sulfotransferase inhibitor and the side effect of nephrogenic diabetes insipidus in Li-treated patients may be due to BPNase inhibitory activity of Li [22]. PGM, an enzyme involved in glycogenolysis, is also recently known to be inhibited in humans by Li therapy [25].

Pleotropic effects of lithium

Immunity is the most useful mechanism which helps to reduce the pathogenic influence upon the body. Daily, we come across many pathogens entering into a human body in a day-to-day life but the defence system in the body makes an effort to kill the pathogens and protect us from them. Li treatment increases phagocytic activity of macrophages, interferon levels, enhanced T-cell proliferation and immunoglobulin synthesis by B lymphocytes at higher doses of treatment [9]. These immunological effects are probably due to depletion of cAMP by inhibiting adenyl cyclase enzyme. Thus, Li has a potent ability in treating inflammatory disorders, auto immune diseases, infectious diseases and cancers.

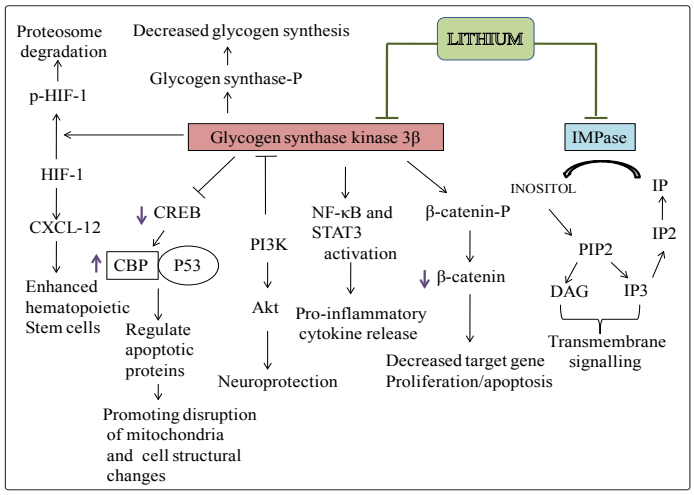

Figure: Multiple pharmacological effects of lithium [11, 26, 27].

Lithium and immune cell types

Macrophages act as 'pathogen sensors' by initiating the inflammation and adaptive immune responses and, thereby, eliminating the pathogens [28]. Monocytes turn to macrophages which originate from the progenitor cells and peripheral mononuclear cells (PMNCs) in bone marrow. Macrophages have a key role in an effector cell by initiating the Th1 immune responses, and also recently it is found that macrophage predominated by IL-4-induced T helper type 2 humoral immune response by IgG class switching [29]. In vivo

study conducted by Turner and Allalunis, showed the effect of Li carbonate on healthy volunteers produced CSA production of mononuclear cells and is calculated by its ability to prompt granulocyte-macrophage colony development by the third day of therapy [30]. Effect of Li on GSK3β is involved in the STAT3 activation in macrophages and astrocytes [31]. Li also induces macrophage apoptosis by inhibiting IMPase unaffecting endothelial cells, and vascular smooth muscle cells, thereby it is suggested for putting off atherosclerotic plaque destabilization showed that Li is involved in apoptosis and necrotic type of death due to DNA fragmentation and caspase activation in the Mycobacterium kansasii-infected macrophages, but no detrimental effect on uninfected cells [32- 34]. Patients with essential hypertension, insulin-dependent diabetes and nephropathy showed increased Na^{+}-Li^{+} counter transport in red blood cells [35, 36]. Intracellular sodium concentration and sodium-Li counter transport have no significant effect on the dietary sodium restriction [37]. SH-group reagents inhibit Na^{+}-Li^{+} exchange, thereby reducing the turn over number of the exchange system by making a conformational change in the SH group of a membrane protein, through binding of red cell external Na^{+} or Li^{+} [38]. In vitro studies of Harker and others have reported that by promoting CSA synthesis Li enhanced the granulocyte production but not in the absence of CSA and this property of Li were arrested by puromycin which specifies that this action requires active protein synthesis [39, 40]. Increased Ca^{+2} levels via activation of G-protein stimulated by neutrophils and platelets in manic-depressive condition has been known to be compensated by diminished Ca+2 responses of patients undergoing Li therapy are certainly due to decreased agonist prompted conglomeration of inositol phosphates [41]. Azzara et al. have reported the in vivo effectiveness of Li in treating Shwachman-Diamond syndrome where impairment of neutrophil function and intermittent neutropenia are present in this condition. Li being capable of inducing leukocytosis and modulating the microtubular system of leukocytes is very useful for this syndrome because of the lack of therapy till date [42]. Li induced granulopoiesis by rising vitamin B12 binding in patients. In vitro, it stimulates the increased granulocyte colony forming units [43]. CBZ induced toxicity by inhibition of murine and human bone marrow-derived granulocyte-macrophage (CFU-GM), erythroid (BFU-E), and megakaryocyte progenitor (CFU-Meg) cells is reversed by stimulating bone marrow function at the optimal Li dose (1.0 mM) but only time dependently i.e, no protective effect is observed after 24 hour delayed addition of Li [44]. Li decreases stromal-derived factor-1(SDF-I) by downregulating the CXCR4 expression of neutrophils which plays a vital role for retention of hematopoietic cells within the bone marrow and this may be one of the mechanisms of Li for causing neutrophilia [45]. Li carbonate at the dose of 900 mg given daily for patients with Felty's syndrome (Rheumatoid arthritis with granulocytopenia) showed a dramatic rise in peripheral blood granulocytes [46]. Regulation of TNFα expression by GSK3 inhibition and prolonged activation of p38/MNK1/eIF4E pathway of mRNA translation was a potentiating role of Li on inflammatory diseases [47]. Significant involution of the thymus gland and loss of thymic lymphocytes upon chronic treatment with Li chloride was detected in both normal and adrenalectomized mice, and all these effects of Li were proved to be only on the thymus gland and not mediated by adrenocortical mechanisms by observing the increased corticosterone levels and also having no change in adrenal weights in normal mice [48]. From the outcome of clinical study on idiopathic thrombocytopenic patient carried out by Sakic and Dadasovic illustrated that Li is able to induce early activating factors for megakaryocytic lineage such as IL-3, IL-11 and thrombopoietin (TPO). It is also known to increase the FLT-3ligand, which is significant for maturation of megakaryocytes and thus confirming its competence in increasing the thrombocytic count [49]. According to Bille et al. ,the mechanism behind the elevated thrombocyte counts in Li therapy was hypothesized to be either its stimulatory effect on granulocyte and thrombocyte precursors in the bone marrow or its ability to differentiate stem cells for granulopoiesis and thrombopoiesis [50]. Dendritic cells (DCs) are referred to as 'professional' antigen presenting cells (APCs) for its capability to induce primary immune response on naive T lymphocytes. Dr. Ralph M. Steinman was awarded the Nobel Prize in physiology or medicine in 2011 for discovering the chief role of dendritic cells in regulation of adaptive immune response [51]. B cell activation and differentiation along with maintenance of immunological memory via follicular DCs (FDCs) serves as an ultimate property in host defence system [52]. Role of GSK-3 was investigated using an in vitro model of human monocyte-derived DC differentiation because of multiple actions on cellular differentiation, apoptosis and motility. From the results, GSK3 was shown to inhibit macrophage development and suppresses spontaneous maturation during differentiation of DCs. It is also able to elevate IL-12, IL-6 and TNF-α secretion. IL-10 levels are partially inhibited. GSK-3 increases mRNA expression of IL-12p35 further producing IL-12p70 (pro-inflammatory cytokine) by assimilating the promoting and diminishing pathways concerned in pro-inflammatory DC differentiation and activation [53]. Functional and phenotypic DC parameters have been investigated under the Li therapy. In vivo results showed to restore impaired DC differentiation defect, and activated the monocyte-derived DCs, thereby stimulating the autologous T cells but in contrast the suppressive effects were detected by reducing the monocyte differentiation into DCs with elevating the monocyte marker CD14 and decreasing the levels of DC-SIGN and CDIa, in vitro [54]. This suppressive effect may be probably due to the elevated monocyte production of TH2 cytokines and lymphocytes [55]. Partial rescuing in dendritic atrophy of the mutants' hippocampal pyramidal neurons by Li therapy can be a probable reason for improvement in cognitive dysfunction in spinocerebellar ataxia type 1 (SCA1) condition. Stress-induced reduction in dendritic length was prevented by Li in CA3 hippocampal neurons. Downregulation of isoprenylcysteine carboxyl methyltransferase (Icmt), which was an early marker in mutant ataxin1 (ATXN1) toxicity, was shown to restore these levels by Li [56]. Microarray-based gene expression analyses were observed on Li-treated MoDCs and microglia separated from Li-treated mice by using ELISA, quantitative PCR and immunostaining studies. Expression of inflammation and chemotaxis-relevant genes produced differing effects upon Li treatment, by significantly over-represented in MoDCs, whereas no specific genes were over-represented in microglia. Li via GSK3 inhibition significantly induced the third component of complement (C3) production in both MoDCs and microglia. Only the differentiated monocytic cells induced C3 production but not circulating monocytes in Li therapy, which was regulated by GSK-3. This ability of Li to induce microglial C3 production may possibly be useful in neuroprotection in regulation of mechanism involved in interaction between microglia and neurons [57]. Feskeet al., reported in his clinical study on SCID patients have shown impaired activation of transcription factor NFAT, which cause a severe defect in T-cell activation and cytokine transcription affecting T cell and B cells. Mutations in IL-2, JAK-3, the protein tyrosine kinase (ZAP-70, CIITA and RFX5), the epsilon and gamma

chains of CD3 have been noticed. Loss of NFAT activation is not by mutation in the phosphatase calcineurin or in NFAT protein expression of T cells but it is due to the severely compromised T cell activation by nuclear import of NFAT. LiCl therapy in SCID patients achieved nuclear translocation of NFAT by inhibiting nuclear export and also involved in enhancing cytokine gene transcription by initiating calcium signalling [58]. Increased activation of amygdale hypertrophy of dendrites in the chronic stress condition can be reversed by Li treatment. Length and complexity of neuronal dendritic arbores in the amygdala were compared for both treated and untreated rats which were restrained for 21 days. Golgi-Cox impregnation and three-dimensional neuron tracing were used for quantification. Stress influenced elevations in dendritic branching of amygdalar pyramidal neurons were found to reduce the total dendritic length by 18% and the number of dendritic branch points by 21% under Li therapy, whereas no alteration was observed in Li treated control (non stressed) rats. Thus, prevention of stress-induced dendritic remodelling in the amygdala by Li was detected via stabilization of excitatory neurotransmission in patients with bipolar disorder [9]. In the study performed by Seong S. Shim et al., change in synaptic plasticity upon Li treatment was determined. Effect of four-week Li treatment in the dentate gyrus (DG) and hippocampal area CA1 regions of young adult rats on the amount and distribution of dendritic branches using Sholl analyses (method of concentric circles) was scrutinized. After completion of treatment, hippocampi were isolated and stained using rapid Golgi staining technique. In both the proximal halves of dendritic trees of DG and apical CA1 regions, it resulted in the increased amount and distribution of dendritic branches but decreased branching was observed in the distal half of both the regions in the same treatment. But the total density of dendritic trees was not altered. Thus, rearrangement of neuronal morphology was observed in both the DG and apical CA1 from chronic Li treatment by increasing dendritic branching and distribution in the regions receiving major afferent input [59].

Lithium and inflammation

Li shows anti-inflammatory activity by reducing pro-inflammatory phospholipase A2 enzyme production which is useful against many diseases. PGE2-mediated inhibition of GSK3 exerts regulation of inflammation by enhancing IL-10 levels and inhibiting the production of TNF-α, IL-6 and CCL3/4 [14]. Li treatment effectively reduced IL-6, IFN-γ and IL-17 production by splenocytes in an autoimmune encephalomyelitis (EAE) mice induced by myelin oligodendrocyte glycoprotein peptide (MOG35-55) immunization. These evidences made an approach for targeting GSK3 inhibitors against autoimmune and inflammatory diseases [60]. Li at a dose of 50 mg/kg suppressed the polymicrobial sepsis triggered pro-inflammatory cytokines and oxidative free-radicals of the tissue injury in the lungs induced by cecal ligation and puncture. Apart from that, the GSH, SOD and catalase levels were found to increase upon pre-treatment with Li, by which, it can be assumed to nullify the oxidants release due to inflammation. In the ex vivo assay, effect of Li on whole blood cultures resulted in increased Th2 cytokines (IL-4 and IL-10) and decreased Th1 cytokines (IFN-γ and IL-2). Li significantly decreased the inflammatory cell infiltrations in cecal ligation and puncture (CLP)-induced sepsis, whereas prominent dense and nodular forms of infiltrations are found in the CLP group. Li also proved to inhibit neuro- inflammation in a hypoxia-ischemia rodent model by inhibiting IL-1β and monocyte chemotactic protein-1. Lipopolysaccharides (LPS)-induced production of NO and PGE2 were attenuated due suppressed expression of iNOS and COX-2 upon treatment with Li. Inflammatory mediators produced by mouse primary astrocytes and microglial BV-2 cells were also inhibited by decreasing the transcriptional signalling of NF-kB [61]. Topical use of Li gluconate was found to be beneficial in seborrheic dermatitis (SD), which was an inflammatory skin disease. Effect of Li on keratinocytes at 1.6 mM concentration enhanced TNF α production, whereas higher concentration (5 mM) significantly decreased TLR2 and TLR4 expression with an increased expression of IL-10. IL-10 possess' multifunctional capabilities like inhibition of antigen presenting cells and CD4+ T cells proliferation. Th2 cellresponses to microorganisms are regulated by IL-10 [62]. GSK3 is known to regulate inflammation in both peripheral and central nervous system.Li by GSK3 inhibition is known to treat arthritis and peritonitis in mice. Li at the dose of 10 mM significantly reduced LPS-induced inflammation by suppressing the production of TNF-α, IL-1β, PGE2 and NO in primary glia cells but at 1 mM it did not show any therapeutic effect in reducing inflammation. Interestingly, the anti-manic effect of Li is mainly observed when given prophylactically, and Li needed in the post-treatment of brain inflammation may be higher when compared to prophylactic treatment [63]. Li inhibits the prostaglandin production. Li therapy also enhances 17-hydroxy-docosahexaenoic acid (17-hydroxy-DHA) levels having anti-inflammatory property [64, 65]. There are many controversial results in NO synthesis of Li therapy. However, the anti-inflammatory effect of Li proved to decrease NO levels, but some studies showed increased iNOS expression in increasing NO concentration and the similar case with TNF-α [66]. GSK3 promotes pro-inflammatory cytokines by stimulating NF-kB transcriptional factor, aggression and impulsivity in depression patients hence Li being GSK3 inhibitor is known to suppress inflammation, aggression and suicidal behaviour [67]. Neurodegeneration of traumatic brain injury was reduced by Li at the dose of 2 and 3m Eq/kg. Results in the study after 3 days and 3 weeks post injury reported that Li significantly reduced lesion volume, neuronal death and microglial activation [68].

Lithium and haematopoiesis

Li stimulates granulocyte macrophage colony stimulating activity (GM CSA) production via macrophage or T-cell mechanism (s) according to the studies performed in dexter long-term liquid cultures [69, 70]. Li also acts on pluripotent stem cells, platelet production and megakaryocytes [71]. Li carbonate at a dose of 1milliequivalent per litre (mEq/l) of solution is shown to increase bone marrow CFUs and granulopoiesis [72]. PI3Kand mTOR signalling is regulated by GSK3. Enhanced hematopoietic stem cells (HSC) pool was observed upon GSK3 inhibition in the presence of rapamycin by over expression of stabilized β-catenin [73]. Hypoxia-inducible factor-1 (HIF-1) stimulates transcription of CXCL12, gene related to hypoxia. Li inactivation of GSK3 results in enhanced HIF-1 levels and marrow trophic niche function by increasing CXCL12 resulting in increased production of neutrophils, platelets and CD34+ HSC. Li levels are maintained at 0.8–1.2 mEq/l at which AKT phosphorylation has been prominently observed. But Li, at a dose of 2 mEq/l, directly inhibited (50%) GSK but the dose is, however, less tolerated. Sitagilptin, an anti diabetic drug enhances the inhibition of CXCL12 destruction [26]. Because in Li therapy total leucocytic counts are increased, Kleinerman et al. aimed to identify whether or not monocytic secretions like TNF-α or IL-1 mediated effects are produced in monocytes by Li treatment [74]. Human normal monocytes (2×10^5 cells) were then incubated for 24 hours with Li (0.05–50 mM), medium (negative control) and LPS (positive

control), and results were obtained as that only TNFα-increased levels are secreted by 4-times increase in TNFα mRNA (5-10 U/ml) and not IL-1. It is also reconfirmed by neutralizing TNFα activity by monoclonal antibody against human TNFα but not against human albumin. This effect of Li to stimulate monocytes to exude TNFα is not observed in other alkali metals (rubidium and cesium). Hence, this transcriptional augmentation of TNFα production by monocytes may be one of the possible mechanisms for granulocytosis by Li [74]. As many studies proved that Li salts are known to decrease the intensity and continuance of neutropenia in cancer patients, Merendino et al. tried to understand the effect of interleukin-15 on Li therapy. IL-15 is a cytokine having heamopoietic and antitumor activity triggered by NK, CTL, LAK cells, and LiCl therapy on monocytes taken from metastatic and non-metastatic breast cancer patients resulted to enhance the IL-15 release mainly from non-metastatic patients and it is clear that this effect may hinder the immunosuppressive state of cancer patients. Increased IL-15 levels are observed in both LPS- and LiCl-treated monocyte cultures compared to simple LPS-treated cultures ($p<0.0001$).The effect of Li carbonate in the mechanistic studies of increased myelopoiesis has been investigated by Verma and group on monocyte macrophage and T-lymphocyte (TL) obtained CSA, in vitro. This resulted in increased synergistic CSA elaboration with macrophage and TL interaction, only at higher concentration (2m Eq/l) and about 62% of macrophage and TL rosettes are observed upon Li treatment as compared tothat of untreated ones whichhaving only 21%. In further experimentation they proved that Li is able to antagonise concanavalin (Con-A) effects of suppressing T cell and thereby enhancing the CSA development, and can be useful in suppressor T cell associated neutropenic disorders [9]. To investigate whether or not the changes in peripheral blood T cell subsets have role in Li-induced granulocytosis, Besana et al. conducted an experiment by administering Li carbonate to 10 subjects over 14 days. Prior to administration of drug (on Day +1) differential leucocyte counts, T, B, T helper and T suppressor lymphocyte enumerations are determined and the same was performed on Day +7 and Day +14 during therapy. Results obtained showed significant elevation in neutrophil levels, and all other cell types were not altered significantly compared to control group. Li has direct, immediate action with quick onset and loss of action on granulopoiesis by modulating intracellular nucleotides [75]. In vitro proliferation of human erythroblast, and T and B lymphoblast leukaemia cells was observed to be induced by LiCl treatment, and also the same drug at the concentration of 5×10^{-4} M enhanced colony formation of myeloid leukaemia cell lines (HL-60 and KG-1). Li also enhanced colony formation of MOLT 4 (T-lymphoblast cell line) and IM-9 (B-lymphoblast cell line) at 10^{-6} and 10^{-3} M of LiCl, respectively. Apart from that LiCl is known to enhance murine or human K-562 erythroleukaemia cells colony formation, which serves as key therapeutic agent used in haematological malignancies. Li also elevates the mitogen-induced lymphocyte proliferation by modulating the cAMP dependent actions [76]. Li having low mutagenic and carcinogenic properties is still used as an effective therapy for depression but prolonged uptake of Li more than 2 mM can lead to serious neurological symptoms and brain damage.Liis known to induce granulocytosis and boost immune functions. Li affects phosphorylated inositides and produces white blood cells. Li at 50 mg/kg increases erythrocytes and hematocrit, and also enhances the functions of lymphocytes and macrophages in rats. Li at stimulates hematopoietic stem cells directly but upon proliferative stress, it can be associated with depletion of stem cells and their replication in a dose-dependent manner. Li can boost the immune function by increasing lymphocyte and human mononuclear cells activity against mitogens. Topical administration of Li succinate plus zinc sulphate and Li gluconate are found to be useful in seborrhric dermatitits because of its low percutaneous penetration. Granulopoietic differentiation arrest mediated by interferon was prevented by Li. Lymphopenia and increased lymphocyte activity induced by Li explains both positive and negative effects on immune system. However, Li doesn't show any effect in the normal individuals [77]. Li enhanced the growth of HL-60 cells at the range of 2 to 10 mM, but optimal growth was noticed at 5 mM. In vitro studies at this concentration also showed increased growth of bone marrow cells and human T cells. Li is more effective on progenitor cells rather than cellsthat have already reached maturity, so it is assumedthat Li may perhaps acts similar to that of physiological growth factors. Effect of Li at higher concentrations, subsequently arrested the [3H] TdR incorporation, which evidenced the link between DNA synthesis and cytotoxicity [78]. Action of Li on granulopoiesis and lymphopenia may be due to the direct action on bone marrow progenitor stem cells and inhibition of thymus dependent lymphocytes by reducing cyclic AMP. Increase in eosinophil and platelet counts are also noticed upon treatment with Li; it also plays an important role in treating neutropenia in cancer patients who undergone chemotherapy and radiation. Due to resemblance of ionic radii and comparable charge densities of Li and divalent cations like sodium and calcium, Li may compete with them in tissue fluids and cell proliferation. This can also be the reason for inhibition of erythropoiesis in Li therapy. After prolonged exposure to Li, accumulation of choline in erythrocytes occurs due to reduction of neurotransmitter release in neuromuscular apparatus, which further converts to acetylcholine and stimulate erythropoiesis [79]. Cyclophosphamide (200 mg/kg)-administered mice pre-treated with Li carbonate at a dose of 35 µg/kg showed increased stem cell, neutrophil and platelet count. Hence, from this confirmation, Li can be used to recover the blood cell count when the agents likely to suppress haematopoiesis are administered [80]. LP-BM5 MuLV (MAIDS)-infected immuno deficient mice, when treated with Li carbonate (1 mM) in drinking water suppressed the late stage disease conditions like lymphadenopathy, splenomegaly and lymphoma, and also prolonged the survival of animals. Li regulates the differentiation of pluripotent and committed progenitor cells. Pancytopenia developed in retroviral infections, which was further exacerbated by certain antiviral therapies like zidovudine was significantly reduced in the animals after receiving Li [81]. Tolerability of patient towards Li therapy was very good and is cost effective. Thus it can be easily used in cancer patients suffering from chronic leucopenia caused by adverse effects of tumour destructive therapy. CSF concentration can be increased significantly by Li, in low a dose, which stimulates proliferation of human mononuclear leucocytes. Li showed effect(s) on B lymphocytes and plasmocytes with ten-fold elevated immunoglobulin synthesis and effect of T lymphocytes increased production of IL-2. An elevated IL-2 level by Li is due to decreased intracellular cAMP content-induced increased lymphokine-activated killer cells (LAKs) activity [82]. GM-CSF and IL-6 are known to be induced by Li salts, which may also form part to reduce the risk of bleeding and platelet recovery for patients suffering from thrombocytopenia. For the treatment of patients with thrombocytopenia, Li carbonate at the dose of 800–900 mg/ per day for at least 5–10 days, followed by a one-week period without Li therapy can be recommended. Synergistic effects were observed with the concurrent treatment

with IL-11 or thrombopoietin. Therefore, owing to the wide applications of Li in preventing infection and bleeding, in the near future, it is hoped to become an essential part to the prophylactic approach in oncology [9]. Joyce, R. A. tried to examine the haematopoietic changes by administering LiCl (60–600 mg/kg, daily) to mice. In his observations, it is revealed that Li increased the concentrations of CFU-GM as well as progenitor cells for megakaryocytes (CFU-M) and erythrocytes (BFU-E and CFU-E) along with marrow neutrophil production. Megakaryocyte progenitor cells were cultured by suspending the cells in 10% pokeweed mitogen-stimulated mouse spleen cell CM (PWCM) along with 1.8% methyl cellulose containing culture medium CMRL-1066 and 15% fetal calf serum, and incubated at 37°C in 10% CO_2 for 9 days. Colonies containing 2 or more megakaryocytes were counted and quantitated, separately, for each mouse. Colonies are smeared between cover slips and stained with Wright's stain by separating them with a Pasteur pipette. LiCl at a dose of 240 mg/kg, administered daily, significantly elevated the platelet concentrations by day 5 ($P<0.05$), and by day 15 these values returned to control [84]. Chatelain et al. have performed an in vitro study to evaluate the effect of LiCl on early megakaryocytopoiesis and murine marrow megakaryocytic progenitors. LiCl (2 mM) in the splenic cell cultures in the presence of pokeweed mitogen (PWM-SCM) produced significantly enhanced CFU-M (157±8%) and CFU-C (183±8%)-derived colonies compared to control cultures. To prove the hypothesis of Li's ability for the enhancement of early hematopoietic progenitors may possibly be due to the CSA production rather than its direct effect on stem cells, cyclosporin-A (3 µg/ml), a T-lymphocyte function inhibitor was added under the same conditions to suppress CSA production. Li-induced enhancement of progenitor cells was abrogated by CyA, and no effect was observed when added alone on colony formation. These results confirmed the CSA production (local) and requirement of functional T-lymphocytes by Li may probably owe to enhance of early megakaryocytopoiesis and granulocytopoiesis [84].

Lithium and apoptosis

Apoptosis is condensation of nuclear chromatin and cell body along with shrinkage of nuclear membrane. Neuroprotective effects of Li by activation of PI3K are mediated by $[Ca^{+2}]i$ without influencing influx of extracellular Ca^{+2} release through the phospholipase C (PLC) pathway. Antiapoptotic activity of Li can be reversed by selective Ca^{+2} chelator, BAPTA-acetoxymethylester [85-87]. Li therapy attenuates excitoxicity and neuronal injury mediated by NMDA receptor, and deprivation of oxygen and glucose. Apoptosis was interfered by elevated $[Ca^{+2}]i$ level through activation of PI3-K by AKT phosphorylation of Thr308 by activating Ca2/calmodulin-dependent protein kinase [88]. Developmental neuroapoptosis induced by ethanol, and an anaesthetic drug-provoked ERK phosphorylation was potently diminished by Li (3 mEq/kg) in a long lasting manner for about 6 hs [89]. Lithum at the dose of 1 mM/kg suppressed the apoptotic events (activated caspase-3 expression and DNA fragmentation) in ischemic brain 48 hs after Middle Cerebral Artery occlusion (MCAO). Elevated expression of Bcl-2 (anti-apoptotic protein) and diminished concentrations of P53 and Bax (pro-apoptotic protein) was shown in the chronic treatment of Li, both in vitro and in vivo. Being a proapoptotic kinase, GSK3β over expression leads to neuronal cell death. Li hampers pro-aptototic signalling by inhibiting GSK3β [90]. Repression of drug-induced CD95 expression and caspase-8 activation along with augmented disruption of p53 destabilization explained the anti apoptotic effect of Li against etoposide and camptothecin-induced apoptosis [91]. Potassium deprivation-induced apoptosis in cerebellar granule cells was suppressed by Li with the activation of caspase 3 inhibition and increased anti-apoptotic Bcl-2 and Bcl-XL levels in brain. The Bcl-2/Bax protein ratio is increased five-fold upon Li treatment. Endoplasmic reticulum containing apoptosis-regulating proteins also contributed an important role in anti-apoptosis of Li [92]. Thymocytes after several stages of maturation convert to functional T cells. After initial stage of cortex of the thymus with TCR beta chain (beta selection) and functional interactions with MHC (positive selection), in medulla final maturation of thymocytes occur and release into blood stream as mature T cells. Foxp3, transcription factor is involved in the regulation of glucocorticoid-induced TNF receptor (GITR) expression in T cell. NF-kB and NFAT, the positive and negative regulators of GITR expression, respectively, contribute for cell survival. LiCl enhances NFAT activity and curb TCR-mediated GITR up-regulation protect T cells from TCR-mediated apoptosis [93]. Studies on the hypoxia ischemic mice induced by irradiation have shown to suppress neural progenitor cell apoptosis and improve learning deficits in the granule cell layer of hippocampus. Degeneration of neural stem and progenitor cells, and malignancies caused by irradiation can be prevented, and tumour cells can be prone to caspase activation during Li therapy [94]. In contrast, Li-induced neurotoxicity was explained by increase in NFAT/Fas (death receptor) signalling and attenuated release of cytochrome c binding to Apaf-1 and Bax translocation from mitochondria via GSK3β inhibition, which promotes neuronal apoptosis and motor deficits. This mechanism of Li-induced apoptosis was prevented by cyclosporin A administration or in Fas-deficient lprmice [95]. LiCl enhanced the cytotoxic and apoptotic effect of vinorelbine when given in combination by decreasing BrdU-LI and cAMP levels. Significant induction of apoptosis with inhibition of colony formation and spheroid growth was observed [96]. LiCl augmented TNF-related apoptosis-inducing ligand (TRAIL)-induced apoptosis through caspase activation via death receptors DR4 and DR5 at protein and mRNA levels, inhibition of cdc2 activity and G2/M arrest provoked by inhibition of JNKs significantly in a dose-dependent manner in A549 cells [97]. Li-mediated modulation of apoptosis via caspase activation, DNA fragmentation and ROS-production in Mycobacterium kansasii-infected bone marrow-derived macrophages (BMDMs) potently enhanced infected cell death and intracellular growth of infection, whereas, uninfected cells are not affected by the addition of Li. Reduction in bacterial growth and enhancement of apoptosis with Li treatment was abrogated by preincubation with N-acetylcysteine (NAC), ROS scavenger which suggests the importance of ROS in killing bacillary viability [34]. Macrophage cell death induced by Li treatment stabilizescollar-induced atherosclerotic plague formation via IMPase inhibition leading to decreased IP3 levels and produce intense signal transduction effects in cells without changing viability of SMCs and endothelial cells [33].

Therapeutic evidences of lithium by mainly inactivating GSK3β in various infectious diseases

Antibacterial activity

GSK3β is the central regulator for the response to bacterial stimuli acting through innate immune system. Pattern recognition receptors primarily respond to bacterial infection by initially activating the innate immune cells with a subsequent stimulation of adaptive immune system. Inactivation of GSK3β by suppressing MyD88-dependent cytokine production has potential effect in controlling

inflammatory diseases caused by bacteria. Phospho-inactivation of GSK3β induced by prostaglandin E decreased the production of CCL3/4 and a number of pro-inflammatory cytokines by which the eukaryotic chemotaxis modulation of inflammatory response to gram negative bacteria can be explained. Many studies have proved that GSK3β suppressed the iNOS expression in TLR-dependent manner to regulate the inflammatory cytokines according to the disease condition [98]. Burkholderia pseudomallei, cause of melioidosis, was found to increase the survival, modulate the inflammatory cytokines, and also showed to clear the bacteria in various organs in infected mice with hyperglycaemia after GSK3β inhibition because the survival and replication of bacteria within hyperglycaemic PBMCs (peripheral blood mononuclear cells) mainly requires the GSK3 dependent NF-kB activation. LiCl acted as immunomodulator for balancing inflammatory function upon targeting the innate immune system [99]. LiCl was also known to ameliorate Mycoplasma hyopneumoniae infection which affects the swine industry. In vitro study of PK-15 cells infected with M. hyopneumoniae infection, LiCl at the dose of 40 mM decreased the production of nitric oxide, reactive oxygen species and apoptotic cell death by reducing the caspase 3 activity [100]. LiCl was found to suppress Mycobacterium kansasii infection effectively by mechanism involving intracellular bacterial scavenging mediated by N-acetylcysteine and enhanced macrophage apoptosis in caspase- and TNF-dependent manner. DNA fragmentation and ROS enhancement of infected cells apart from normal uninfected host cells with the treatment of LiCl also increased the antibacterial effect [34].

Antiviral activity

LiCl possess antiviral activity by inhibiting viral DNA synthesis at the concentrations allowing the host DNA replication. The other mechanisms including inhibition of protein synthesis by replacing enzyme cofactor magnesium ion by Li, alteration in prostaglandin E, macrophage and lymphocyte physiology, and inhibition viral DNA polymerase and free fatty acid synthesis [101]. Neuroprotective effect of Li is known for its subsequential barrier of beta catenin and tau phosphorylation through GSK3β inhibition. Depending on this Dou et al. performed a study on murine human immunodeficiency virus-1 (HIV-1) encephalitis (HIVE) for exploring neuroprotective mechanisms of Li. Results confirmed the neuroprotection by Li via inhibition of GSK3β and PI3K/AKT pathways protected from neurotoxins released from the HIV-infected monocyte-derived macrophages (MDMs). Mechanism of Li by reducing phospho-Tau Ser 202, phospho-beta-catenin and GSK3β restored the loss of microtubule associated protein-2-positive neuritis and synaptic density associated with HIVE [9, 102]. LiCl also proved to treat Enterovirus 71 (EV-A71) by suppressing the viral replication and decrease the viral progeny load. Targeting the host inflammatory response by attenuation of high levels of inflammatory cytokine production was the key factor for antiviral therapy of LiCl via AKT-GSK3β signal pathway [103]. LiCl was found to restore host cell protein synthesis (mainly plasminogen activator inhibitor 1 (PAI-I) and thrombospondin while viral polypeptide synthesis was reduced in herpes simplex virus that was dependent on viral dose and concentration of Li used. Functions of PGE1 were blocked by Li, which further helps in averting the recurrence of disease [104]. Avian infectious bronchitis virus was prevented with LiCl treatment by inhibiting the cell infection, and genomic RNA and sub genomic mRNA synthesis with no observation of apoptosis in the infected cells, in vitro [105]. Entry and viral DNA replication of porcine epidemic diarrhoea virus (PEDV) in Vero cells was suppressed by LiCl in a dose-dependent manner. LiCl also inhibited both early and late cell apoptosis provoked by PEDV [106].

Anti-parasitic activity

GSK3 inhibitors are known to suppress the plasmodial species. Non ATP-competitive GSK3 inhibitor, LiCl has shown curbing potential when tested in erythrocytes against cultures of P. falciparum 3D7 ex vivo with an IC50= 25.468 μM. Both signalling pathways, GSK3 and MAPK, are known to control the pathogenesis of malaria, and recently it was proved that inactivation of GSK3 may also take place due to the p38 MAPK phosphorylation. It was reported that recombination of the P. falciparum GSK3 was inhibited by GSK3 inhibitors. [107]. LiCl alone suppressed the progression of P. berghei infection in a rodent malaria model; LiCl inactivate GSK3 by inhibiting the phosphorylation of serine residues or indirectly enhance the inhibitory phosphorylation of GSK3 [108]. LiCl is known to affect the cell division and metabolism of the parasite. It is reported that LiCl at the dose of 300 mg/kg suppressed the P. berghei infection in a rodent malaria model without causing any toxic effects [109]. Blood-schizonticidal activity of different LiCl combinations (treated for 4 days, daily once from the day of infection) against P. berghei infection (1 x 10^7 IE per mice on Day 0) in Swiss micewas determined. Combined effect of LiCl (300 mg/kg) along with artesunate (10mg/kg) and curcumin (100 mg/kg) reduced parasitaemia significantly about an average of 70 % and 78 % respectively on day +17 with 100% survival rate of animals in each group,whereas all negative control animals were found to dead.Immunomodulatory effects including phagocytic activity, leucocytic count and bone marrow cellularity was also found to increase drastically in these combination doses along with increased pool size of splenic and peritoneal macrophage count (unpublished data). Lihas been reported to show anti-malarial activity by activating protein kinase B, and thereby reversed the memory impairment and motor coordination deficits which can even persist after effective anti parasitic treatment. Neuroprotective effects of Li are mainly through the AKT/GSK3β regulation, which is the key factor for neuronal and cell survival mediated by insulin and growth factor. Parasite load and mosquito life span were found to be reduced by AKT regulation [110].

Others

Li is known to acts as antifungal by preventing Saccharomyces cerevisiae augmentation through inhibiting phosphoglucomutase, which is an essential enzyme for galactose mechanism in a galactose containing media. In another study, Li is tried against Candida albicans from which it was proved that the restrain of hyphal outgrowth and filamentous differentiation of Li may be due to the inhibition of rapamycin (mTOR) signalling pathway [111]. GSK3 inhibitors was also been used for targeting infections against Schistosoma haematobium, S. mansoni, trypanosomatid protozoa, Herpeto monismuscarum and Blastocrithidia culici [109,112].

Conclusions

Immunomodulation is the basic criteria required for effective therapy in various infectious diseases. Exploitation of haematopoietic and immunomodulatory properties of Li may be the right approach for evading the infection. Phagocytosis, apoptosis and anti-inflammation clears the pathogen, and reduces the survival and progression of the infective agent. Li can be used as an adjuvant in combination with the standard therapy for boosting the immune system in order to help destruction of the pathogen. Collective efforts to use this

simple drug in various diseases and exploration of its different mechanistic pathway in experimental research may provide an opportunity to bring out the productive results which are expected to be truly useful to mankind.

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