ACS Chemical Neuroscience

Review

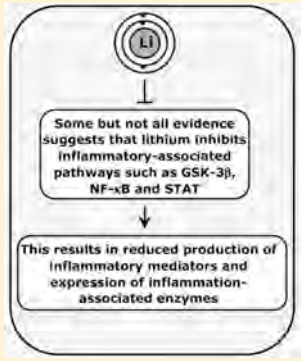
pubs.acs.org/chemneuro

Effects of Lithium on Inflammation

Ahmad Nassar[†] and Abed N. Azab*[,†,‡]

[†]Department of Clinical Biochemistry and Pharmacology, and [‡]School for Community Health Professions − Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva 84105, Israel

ABSTRACT: Lithium is an effective medication for the treatment of bipolar affective disorder. Accumulating evidence suggests that inflammation plays a role in the pathogenesis of bipolar disorder and that lithium has anti-inflammatory effects that may contribute to its therapeutic efficacy. This article summarizes the studies which examined the effects of lithium on pro- and anti-inflammatory mediators. Some of the summarized data suggest that lithium exerts anti-inflammatory effects (e.g., suppression of cyclooxygenase-2 expression, inhibition of interleukin (IL)-1β and tumor necrosis factor-α production, and enhancement of IL-2 and IL-10 synthesis). Nevertheless, there is a large body of data which indicates that under certain experimental conditions lithium also exhibits pro-inflammatory properties (e.g., induction of IL-4, IL-6 and other pro-inflammatory cytokines synthesis). The reviewed studies utilized various experimental model systems, and it is thus difficult to draw an unequivocal conclusion regarding the effect of lithium on specific inflammatory mediators.



KEYWORDS: *Cyclooxygenase, cytokines, inflammation, glia cells, glycogen synthase kinase-3β, lithium, nitric oxide, nuclear factor-κB, prostaglandins*

Bipolar affective disorder (manic-depressive illness) is a devastating mental illness affecting approximately 1−1.5% of the general population.[1] In 1949, John Cade[2] introduced lithium as an effective treatment for mania, and since then it has become the classic pharmacotherapy for bipolar disorder.[3,4] Lithium has an established antimanic effect and prophylactic efficacy against recurrence of affective episodes.[3,4] Moreover, lithium treatment is associated with decreased suicidal death among bipolar patients.[5] However, lithium has a plethora of side effects and has a narrow therapeutic window which necessitates close monitoring of its plasma concentration.

The mechanism underlying the therapeutic efficacy of lithium as a mood stabilizer is not fully understood. Several hypotheses have been suggested to explain its mechanism of action, including depletion of inositol levels in the brain;[6] inhibition of glycogen synthase kinase (GSK)-3β;[7,8] as well as other signaling molecules, neurotransmitters, and cellular pathways that are affected by lithium.[3] Thus, while lithium has a wide range of pharmacological effects, it is not clear which of these is most relevant to its therapeutic efficacy. In recent years, a large body of evidence has accumulated suggesting that inflammation plays a role in the pathological processes underlying bipolar disorder.[9−12] Numerous studies examined the inflammatory profile of bipolar patients most of which revealed that *blood* levels of inflammatory mediators are increased in bipolar patients. For example, a recent comprehensive meta-analysis of 30 studies showed that as compared to healthy control subjects, bipolar patients had an altered blood (plasma or serum) inflammatory cytokines profile.[12] The altered inflammatory profile included significantly elevated levels of interleukin (IL)-4, IL-10, soluble IL-2 receptor, soluble IL-6 receptor, tumor necrosis factor (TNF)-α, soluble TNF receptor-1, and IL-1 receptor antagonist; a trend for significantly increased levels of IL-1β and IL-6; and a nonsignificant difference in IL-2, IL-8, and interferon (INF)-γ levels.[12] However, it is important to emphasize that contradicting results have also been reported and that the evidence regarding peripheral cytokines levels in bipolar patients is not conclusive. Many confounders complicate interpretation of the data obtained in different studies, including heterogeneity of studies' population (age, gender, body mass index, illness duration, treatment status, and disease phase); various cytokines measurement methods and different detection limits of assays; coexisting inflammatory diseases; concurrent use of anti-inflammatory drugs; different timing of blood sampling; among others.[11,12] For example, most of the studies which examined the association between treatment status and blood cytokine levels among bipolar patients reported a nonsignificant correlation.[11,12] On the other hand, some studies found that anti-bipolar drugs significantly altered blood cytokines levels.[11,12]

Although most of the studies that examined the association between inflammation and bipolar disorder focused on blood cytokines levels what is more relevant to the study of psychiatric/neurological disorders is to determine the levels of inflammatory mediators in the *brain*. In this regard, it was found that levels of inflammatory markers were increased in post-mortem brains of bipolar patients.[13,14] For example, Rao et al.[13] found that protein and mRNA levels of several inflammatory markers were significantly increased in post-mortem frontal cortex of 10 bipolar patients as compared to 10 age-matched control subjects.

Special Issue: Current Hypotheses of Lithium's Mechanism of Action as a Neuropsychiatric Medication

Received: February 23, 2014
Revised: April 24, 2014
Published: April 25, 2014

For instance, they reported increased levels of IL-1β, IL-1 receptor, myeloid differentiation factor 88, nuclear factor-κB subunits, and glia cells markers such as glial fibrillary acidic protein, inducible nitric oxide synthase (iNOS), c-fos, and CD11b in bipolar patients.[13] The same authors reported in a subsequent paper[14] that protein and mRNA levels of cytosolic phospholipase A2 (cPLA2), secretory PLA2, cyclooxygenase-2 (COX-2), and membrane prostaglandin E synthase (mPGES) were significantly increased in post-mortem frontal cortex of bipolar patients as compared to control subjects. Consistent with the results from post-mortem studies of bipolar patients, Söderlund et al.[15] found that IL-1β levels were significantly higher in cerebrospinal fluid of 30 euthymic bipolar patients as compared to 30 healthy matched volunteers. Nevertheless, it is worth noting that levels of other inflammatory markers were found unchanged (e.g., neuronal NOS, TNF-α, Ca^{2+}-independent PLA2, and lipoxygenases) or even decreased (e.g., COX-1, cytosolic PGES, and IL-6) in bipolar patients.[13−15] Taken together, these findings suggest that levels of several inflammatory markers are altered in brain of bipolar patients. As seen in the following section, lithium treatment affects the levels of those inflammatory markers, suggesting that this effect of the drug may contribute to its therapeutic mechanism of action.

This review summarizes the effects of lithium on production of inflammatory mediators.

EFFECTS OF LITHIUM ON INFLAMMATORY MEDIATORS

One of the earliest findings linking lithium to the immune-inflammatory system was that it increased leukocytes count among lithium-treated patients.[16,17] Thereafter, lithium-induced leukocytosis had become a recognized adverse effect of the drug, bringing some clinicians to use lithium as a treatment for conditions of leucopenia.[18,19] Herein we review the effects of lithium on production/expression of inflammatory-associated mediators/enzymes focusing on those who were most studied.

Cyclooxygenase−Prostaglandins pathway. Anti-inflammatory properties of lithium started to emerge early in the 1970s in reports in which lithium was found to inhibit the synthesis of prostaglandins (PGs).[20,21] Prostaglandins are pivotal mediators of tissue homeostasis and aberrant regulation of their function may lead to deleterious pathophysiological effects.[22,23] Synthesis of PGs involves PLA_2-mediated release of arachidonic acid (AA) from membrane phospholipids and its conversion to PGs by the enzyme COX.[22,23] Among the known COX enzymes (COX-1, COX-2 and COX-3), COX-2 is recognized as an inducible enzyme the activity of which is *mostly* associated with inflammatory and mitogenic conditions.[22,23] However, in some tissues (such as vascular endothelial cells) it has important physiological functions. The AA-PGs pathway has been extensively linked to brain inflammation and treatment of mood disorders.[9,24−26] For example, Bosetti el al.[27] found that chronic lithium administration decreased AA turnover, COX-2 activity and PGE_2 concentration in rat brain. Consistently, chronic lithium treatment significantly decreased lipopolysaccharide (LPS)-induced elevation in brain PGE_2 synthesis in rats.[28] This study[28] also showed that lithium significantly increased 17-hydroxy-docosahexanoic acid (17-hydroxy-DHA) levels in rat brain. Importantly, 17-hydroxy-DHA has been shown to exert anti-inflammatory properties under different experimental conditions.[29−33] Thus, enhancement of 17-hydroxy-DHA production by lithium attests for another anti-inflammatory effect of the drug. Furthermore, we found that lithium reduced LPS-induced elevation in COX-2 expression and PGE_2 production in rat primary glia cells.[34] Wang et al.[35] also observed that lithium significantly decreased expression of COX-2 and production of PGE_2 in primary cultured astrocytes. Similar to lithium, the mood-modulating drugs valproate,[36] carbamazepine,[37] lamotrigine,[38] and olanzapine[39] have also been found to inhibit COX-2 expression and reduce PGE_2 production. Consistent with a role for PGs in the pathogenesis and treatment of mood disorders, the administration of a selective COX-2 inhibitor (celecoxib) to patients with major depression[40] and bipolar disorder[41] was found beneficial in double-blind, placebo-controlled trials.

Despite these findings, other studies have given inconsistent results. For example, Voutsinos-Porche et al.[42] examined the effect of lithium on COX-2 expression in different brain regions in rats and found that it increased COX-2 expression in the cerebral cortex and hippocampus but did not alter expression in other tested regions. Yuskaitis and Jope[43] observed that lithium did not alter COX-2 expression in microglia cells.

Taken together, these findings suggest that lithium attenuates COX-2 expression and PGE_2 production is some tissues (particularly in the brain, following chronic treatment in vivo) but it has no effect or enhances COX-2 expression in other tissues.

Nitric Oxide Synthase−Nitric Oxide Pathway. The nitric oxide (NO) pathway has also been associated with brain inflammation.[44−46] In the brain, NO is synthesized constitutively in postsynaptic neurons by the enzyme neuronal NO synthase (nNOS).[44] Alternatively, after inflammatory stimuli, NO is produced in glia cells by the enzyme inducible NOS (iNOS).[45] Nitric oxide is an active signaling molecule in the brain associated with multiple cellular processes and signaling pathways.[46] Many studies investigated the effects of lithium on NOS expression/activity and NO production reporting inconsistent findings. A number of studies found that lithium enhances the NOS-NO pathway.[47−53] For example, Bagetta and coauthors[47] found that pretreatment with lithium increased NOS activity in rat hippocampus. Du et al.[50] have shown that lithium increased NOS expression and NO production in primary human and rat hepatocytes. On the other hand, several studies showed that lithium inhibits the NOS-NO pathway.[34,35,43,54−59] Yuskaitis and Jope[43] found that lithium decreased LPS-induced elevation in iNOS expression and NO production in microglia cells. Similarly, Wang et al.[35] observed that lithium reduced the expression of iNOS and production of NO in primary cultured astrocytes. Moreover, there were studies in which lithium was found to lack a significant effect on NOS expression and NO production.[60−62]

Tumor Necrosis Factor-α (TNF-α). TNF-α is a *pro*-inflammatory cytokine. In 1989, Kleinerman et al.[63] showed that treatment with lithium led to a significant, dose-dependent increase in TNF-α secretion by normal human monocytes. The authors suggested that the TNF-α-stimulating effect of lithium may contribute to its induction of granulocytosis in lithium-treated patients. Subsequently, other studies also reported that lithium increases TNF-α production.[64−71] For example, Merendino et al.[64] showed that chronic lithium treatment led to a significant increase in plasma TNF-α levels in neutropenic breast cancer patients. Moreover, Guloksuz et al.[68] reported that plasma TNF-α levels were significantly higher in lithium-treated bipolar patients as compared to medication-free bipolar patients and healthy control subjects.

Although a number of studies reported that lithium stimulates TNF-α synthesis, the majority of the studies which examined the

association between lithium and TNF-α found that lithium reduces TNF-α production.[35,43,72−89] For example, Martin et al.[73] observed that lithium significantly decreased TNF-α production in LPS-stimulated monocytes. Similarly, Wang et al.[75] showed that treatment with lithium decreased TNF-α production in vivo in LPS-treated mice and in vitro in LPS-stimulated kidney cortical cells. Moreover, Albayrak et al.[84] found that lithium diminished serum TNF-α levels in a rat model of sepsis.

Taken together, the summarized studies reveal that the effect of lithium on TNF-α varies under different experimental conditions with most studies suggesting that it inhibits TNF-α synthesis.

Interleukin-1β (IL-1β). IL-1β is a *pro*-inflammatory cytokine. In 1988, Kucharz et al.[90] reported that lithium enhanced IL-1 production in peripheral blood monocytes. Similarly, lithium was shown to enhance IL-1β synthesis in human immature dendritic cells.[69] Despite these findings, most of the reviewed studies showed that lithium inhibits IL-1β production.[34,77,78,82,83,87,89,91−94] For example, Knijff et al.[94] observed that lithium decreased IL-1β levels in LPS-stimulated monocytes of healthy control subjects. We found that lithium reduced LPS-induced elevation in IL-1β secretion in rat primary glia cells.[34]

Interleukin-2 (IL-2). IL-2 is an *anti*-inflammatory cytokine. In 1985, Kishter and co authors[95] reported that lithium treatment enhanced IL-2 production in a lymphocytes culture. Subsequently, numerous studies demonstrated that lithium increases IL-2 secretion.[65,90,96−103] For example, Sztein et al.[96] examined the effect of lithium on IL-2 secretion by peripheral blood mononuclear cells taken from normal male subjects and male subjects with acquired immunodeficiency syndrome. They found that lithium treatment increased stimulant-induced secretion of IL-2 by mononuclear cells. On the other hand, there were studies which demonstrated that lithium does not significantly alter IL-2 levels[68,89] or decreases IL-2 production.[70,104,105] Overall, these data suggest that lithium inhibits IL-2 production attesting for an anti-inflammatory effect of this mood stabilizer.

Interleukin-4 (IL-4). IL-4 is a *pro*-inflammatory cytokine. Relative to other inflammatory mediators, few studies investigated the effect of lithium on IL-4 synthesis. The majority of these studies found that lithium increases IL-4 levels.[68,79,104] However, there were also reports that lithium does not affect[89] or reduce IL-4 secretion.[103]

Interleukin-6 (IL-6). IL-6 is a *pro*-inflammatory cytokine. Many studies demonstrated that lithium attenuates IL-6 production.[43,73,74,77,84−87,105−109] Martin et al.[73] found that lithium decreased IL-6 levels in LPS-stimulated monocytes. Moreover, Beurel and Jope[109] have shown that lithium inhibited IL-6 production in vivo in plasma and brain of LPS-treated mice, and in vitro in LPS-stimulated primary enriched astrocytes. On the other hand, a number of studies demonstrated that lithium enhances IL-6 secretion.[57,64,66,68−70,89,94,98,110−112] For example, Beyaert et al.[98] showed that lithium increased TNF-α-induced IL-6 synthesis in fibrosarcoma cells. Marendino et al.[64] observed that lithium significantly increased plasma IL-6 levels in neutropenic breast cancer patients. Furthermore, in some studies lithium was found to lack a significant influence on IL-6 production.[67,85,86] Taken together, these data suggest that the effect of lithium on IL-6 varies under different experimental conditions.

Interleukin-10 (IL-10). IL-10 is an *anti*-inflammatory cytokine. Most of the studies that investigated the effect of lithium on IL-10 found that it increases IL-10 production,[66,67,69,73,74,80,82,83,86,88,103,104,113] attesting for a strong anti-inflammatory action of the drug. For example, Maes et al.[66] observed that treatment with lithium enhanced IL-10 secretion in whole blood cultures taken from normal volunteers. Similarly, Rapoport and Manji[104] found that lithium increased IL-10 levels in whole blood cultures from normal control subjects. Nonetheless, Matsebatlela et al.[70] and Boufidou et al.[105] reported that lithium decreased IL-10 levels, whereas Guloksuz et al.[68] found that IL-10 levels did not differ between medication-free and lithium-treated bipolar patients.

Interferon-γ (INF-γ). INF-γ is a *pro*-inflammatory cytokine. In 1982, Sharma[114] reported that lithium increased the production of INF-γ in cultures of peripheral blood mononuclear cells. Following this report other studies have also shown that lithium enhances INF-γ production.[65,66,104] However, most of the reviewed studies found opposite results, demonstrating that lithium inhibits INF-γ synthesis.[82,86,87,104−106,115,116] For example, lithium was found to decrease INF-γ levels in whole blood cultures from normal control subjects.[104] Tay et al.[82] showed that lithium reduced INF-γ production in serum and multiple organs of bacteria-treated mice. In summary, most of the reviewed studies found that lithium inhibits INF-γ synthesis, attesting for a possible anti-inflammatory effect.

Other Inflammatory Mediators. Lithium has been shown to influence the levels of other inflammatory mediators (such as IL-1α, IL-1 receptor antagonist, IL-3, IL-5, IL-7, IL-8, IL-12, IL-17, IL-22, and granulocyte-macrophage colony-stimulating factor). However, because few studies examined the effect of lithium on these mediators, they are not discussed further in this review.

Glia Cells. Glia cells (microglia, astrocytes, and oligodendrocytes) have several functions in the central nervous system (CNS).[117−119] Microglia (CNS equivalent of macrophages) and astrocytes help in maintaining brain homeostasis and function by secreting growth factors and inflammatory mediators, by supporting and protecting neurons, and by regulating neuroplasticity and cellular resilience.[117−119] Following inflammatory stimuli, microglia and astrocytes undergo morphological changes and secrete numerous inflammatory mediators such as IL-1β, NO, PGE_2, and TNF-α[34,118,120] which facilitate inflammatory processes in the CNS and regulate production of neurotransmitters. Oligodendrocytes produce myelin which covers axons and facilitates electrical conduction through them enhancing the communication between neurons.[118]

Bipolar disorder has been associated with alterations in glia cells expression and function.[121−123] For example, Rajkowska et al. found that the density of glia cells was reduced in several brain regions in post-mortem brains of bipolar patients, as compared to post-mortem brains of matched control subjects.[121,122] In contrast, Cotter et al.[124] reported that glia cells density was similar in post-mortem brains of bipolar patients and control subjects. Numerous studies examined the effects of lithium on glia cells expression and function in vitro[35,43,57,59,83,125−128] and in vivo in animals.[88,92,105,129−133] For example, lithium was found to inhibit growth of astrocytes while increasing proliferation of microglia cells in vitro.[125] Similarly, lithium was shown to reduce apoptosis and enhance survival of microglia cells in vitro.[134] Moreover, lithium has been shown to increase proliferation of oligodendrocytes, resulting in enhanced myelination of optic nerves in mice.[131] Rocha et al.[129] reported that chronic treatment with lithium increased astrocytes density in rat hippocampus. On the other hand, in a mouse model of Alzheimer's disease, lithium treatment led to a significant reduction in astrocytes and

microglia cells activation.[135] The effects of lithium on glial secretion of inflammatory mediators has been examined in numerous studies.[35,43,57,59,83,88,92,106,132,133] For example, Koriyama et al.[59] found that lithium treatment in vitro reduced expression of iNOS and inhibited activation of NF-κB in microglia cells. Moreover, Yu and coauthors[132] reported that lithium decreased microglia activation and COX-2 expression in brains of mice after a traumatic brain injury. Similarly, lithium was found to reduce microglia activation and attenuate COX-2 expression in rats after intracerebral hemorrhage.[88]

POSSIBLE MECHANISMS UNDERLYING THE EFFECTS OF LITHIUM ON INFLAMMATION

The mechanism underlying the inflammation-associated effects of lithium is not clearly understood. Among the established pharmacological actions of lithium, its inhibition of GSK-3β is the one that has been repetitively reported to alter inflammatory responses of various types. Glycogen synthase kinase-3β is a serine/threonine kinase ubiquitously distributed in mammalian tissues.[136,137] In 2000, Hoeflich et al.[138] demonstrated a strong evidence for a relationship between GSK-3β and inflammation. They found that GSK-3β facilitates the activity of the transcription factor nuclear factor (NF)-κB resulting in an enhanced inflammation in mice.[138] Nuclear factor-κB transcription factors are key regulators of transcription for a variety of genes involved in immune and inflammatory responses.[139] Many subsequent studies confirmed the findings of Hoeflich et al. showing that inhibition of GSK-3β by lithium reduced production of pro-inflammatory mediators under various experimental conditions.[35,43,54,57,59,73−75,77,78,80,82,87,89,93,102,107−109,113,115,140] For example, Martin and co-workers[73] found that GSK-3β inhibition by lithium decreased LPS-induced production of TNF-α and IL-6 while increasing IL-10 level in monocytes. This study also showed that inhibition of GSK-3β attenuated NF-κB activity and decreased the production of pro-inflammatory mediators in mice. Similarly, Zhang et al.[74] observed that lithium inhibition of GSK-3β decreased LPS-induced mortality, TNF-α secretion, and NF-κB activation in mice. Wang et al.[35] showed that inhibition of GSK-3β and NF-κB activation by lithium led to a prominent reduction in pro-inflammatory mediators secretion and suppression of COX-2 and iNOS expression. Importantly, it seems that the GSK-3β (inhibition)-associated anti-inflammatory effects of lithium are not solely due to inactivation of NF-κB.[69,71,108,109,115,116,141] Another downstream target of GSK-3β is the transcription factor signal transducer and activator of transcription (STAT). It was found that inhibition of GSK-3β by lithium resulted in reduced activation of STAT, which was accompanied by a prominent decrease in secretion of pro-inflammatory cytokines.[108,109,115] Despite the accumulating evidence indicating that inhibition of GSK-3β attenuates NF-κB activity (leading to anti-inflammatory effects), opposite results have also been published.[51,112,141−143] For example, Rao et al.[143] showed that lithium inhibition of GSK-3β enhanced NF-κB activity and the increased expression of COX-2.

Overall, the summarized data suggest that GSK-3β plays a pivotal role in the mechanism underlying the effects of lithium on inflammation. Figure 1 presents a simplified model illustrating the association between lithium and inflammation.

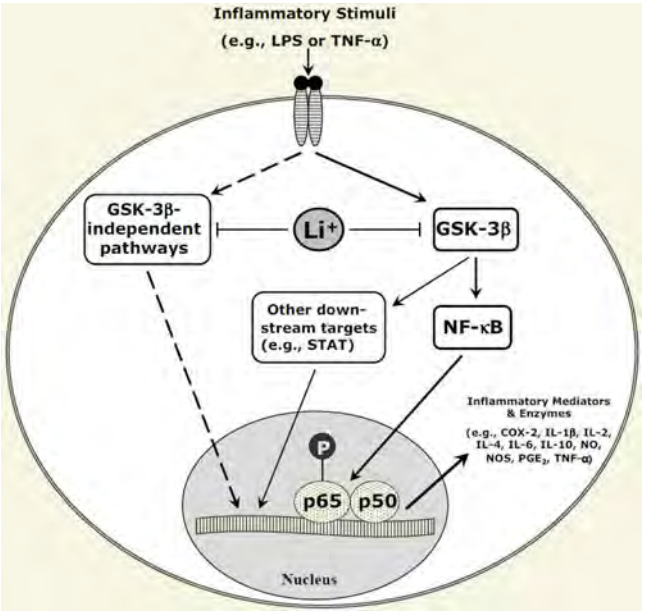


Figure 1. Simplified model illustrating the association between lithium and inflammation. Lithium inhibits GSK-3β, resulting in decreased NF-κB activity. The reduction in NF-κB activity (translocation of p65−p50 to the nucleus and stimulation of its transcriptional activity) leads to attenuated expression of inflammatory-associated mediators and enzymes. Inhibition of GSK-3β by lithium affects other downstream effectors (of GSK-3β) such as STAT, which also results in suppression of inflammation. In addition, lithium alters the inflammatory response through GSK-3β-independent mechanisms. See text for references. Abbreviations: COX-2, cyclooxygenase-2; GSK-3β, glycogen synthase kinase-3β; IL, interleukin; Li, lithium; LPS, lipopolysaccharide; NF-κB, nuclear factor-κB; NO, nitric oxide; NOS, nitric oxide synthase; PGE_2, prostaglandin E_2; STAT, signal transducers and activator of transcription; TNF-α, tumor necrosis factor-α.

SUMMARY

Lithium is the gold standard treatment for bipolar disorder. Despite more than 60 years of clinical use, the therapeutic mechanism of action of lithium remains unknown. In recent years, a large body of evidence suggested that inflammation may play a role in the pathophysiology of bipolar disorder. Moreover, lithium and other mood-modulating drugs have been found to exert anti-inflammatory properties. This article reviewed the data regarding the effects of lithium on inflammation. The summarized data suggest that under certain experimental conditions lithium might have some inhibitory effects on inflammatory pathways. However, there is a large body of data which suggested that lithium has pro-inflammatory effects. The fact that different studies used different experimental model systems complicated the possibility to draw a strong conclusion regarding the anti-inflammatory effects of lithium. Many psychotropic drugs were found to exhibit anti-inflammatory properties. Therefore, it is of great scientific value that future studies examine the effects of different mood-modulating drugs (mood stabilizers, antipsychotics, antidepressants) on inflammation under *identical* experimental conditions in order to search for common anti-inflammatory mechanisms.

AUTHOR INFORMATION

Corresponding Author

*Tel: (972) 86-479880. Fax: (972) 86-477-683. E-mail: azab@bgu.ac.il. Mailing address: Department of Nursing, School for

Community Health Professions, Ben-Gurion University of the Negev, P.O.B. 653, Beer-Sheva 84105, Israel.

Funding

A.N. Azab is supported by a research grant from the Israel Science Foundation

Notes

The authors declare no competing financial interest.

REFERENCES

(1) Narrow, W. E., Rae, D. S., and Robins, L. N. (2002) Revised prevalence estimates of mental disorders in the United States: using clinical significance criterion to reconcile 2 surveys' estimates. *Arch. Gen. Psychiatry 59*, 115−123.

(2) Cade, J. F. (1949) Lithium salts in the treatment of psychotic excitement. *Med. J. Aust. 2*, 349−352.

(3) Belmaker, R. H. (2004) Bipolar disorder. *N. Engl. J. Med. 351*, 476−486.

(4) Gershon, S., Chengappa, K. N., and Malhi, G. S. (2009) Lithium specificity in bipolar illness: a classic agent for the classic disorder. *Bipolar Disord. 11*, 34−44.

(5) Baldessarini, R. J., and Tondo, L. (2009) Suicidal risks during treatment of bipolar disorder patients with lithium versus anticonvulsants. *Pharmacopsychiatry 42*, 72−75.

(6) Berridge, M. J., and Irvine, R. F. (1989) Inositol phosphates and cell signaling. *Nature 341*, 197−204.

(7) Klein, P. S., and Melton, D. A. (1996) A molecular mechanism for the effect of lithium on development. *Proc. Natl. Acad. Sci. U.S.A. 93*, 8455−8459.

(8) Stambolic, V., Ruel, L., and Woodgett, J. R. (1996) Lithium inhibits glycogen synthase kinase-3 activity and mimics wingless signalling in intact cells. *Curr. Biol. 6*, 1664−1668.

(9) Goldstein, B. I., Kemp, D. E., Soczynska, J. K., and McIntyre, R. S. (2009) Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder: a systematic review of the literature. *J. Clin. Psychiatry. 70*, 1078−1090.

(10) Maes, M. (2010) Depression is an inflammatory disease, but cell-mediated immune activation is the key component of depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry 35*, 664−675.

(11) Munkholm, K., Braüner, J. V., Kessing, L. V., and Vinberg, M. (2013) Cytokines in bipolar disorder vs. healthy control subjects: a systematic review and meta-analysis. *J. Psychiatr. Res. 47*, 1119−1133.

(12) Modabbernia, A., Taslimi, S., Brietzke, E., and Ashrafi, M. (2013) Cytokine alterations in bipolar disorder: a meta-analysis of 30 studies. *Biol. Psychiatry 74*, 15−25.

(13) Rao, J. S., Harry, G. J., Rapoport, S. I., and Kim, H. W. (2010) Increased excitotoxicity and neuroinflammatory markers in postmortem frontal cortex from bipolar disorder patients. *Mol. Psychiatry 15*, 384−392.

(14) Kim, H. W., Rapoport, S. I., and Rao, J. S. (2011) Altered arachidonic acid cascade enzymes in postmortem brain from bipolar disorder patients. *Mol. Psychiatry 16*, 419−428.

(15) Söderlund, J., Olsson, S. K., Samuelsson, M., Walther-Jallow, L., Johansson, C., Erhardt, S., Landén, M., and Engberg, G. (2011) Elevation of cerebrospinal fluid interleukin-1ß in bipolar disorder. *J. Psychiatry Neurosci. 36*, 114−118.

(16) Murphy, D. L., Goodwin, F. K., and Bunney, W. E., Jr. (1971) Leukocytosis during lithium treatment. *Am. J. Psychiatry 127*, 1559−1561.

(17) Rothstein, G., Clarkson, D. R., Larsen, W., Grosser, B. I., and Athens, J. W. (1978) Effect of lithium on neutrophil mass and production. *N. Engl. J. Med. 298*, 178−180.

(18) Lyman, G. H., Williams, C. C., and Preston, D. (1980) The use of lithium carbonate to reduce infection and leukopenia during systemic chemotherapy. *N. Engl. J. Med. 302*, 257−260.

(19) Kramlinger, K. G., and Post, R. M. (1990) Addition of lithium carbonate to carbamazepine: hematological and thyroid effects. *Am. J. Psychiatry 147*, 615−620.

(20) Murphy, D. L., Donnelly, C., and Moskowitz, J. (1973) Inhibition by lithium of prostaglandin E1 and norepinephrine effects on cyclic adenosine monophosphate production in human platelets. *Clin. Pharmacol. Ther. 14*, 810−814.

(21) Karmazyn, M., Manku, M. S., and Horrobin, D. F. (1978) Changes of vascular reactivity induced by low vasopressin concentrations: interactions with cortisol and lithium and possible involvement of prostaglandins. *Endocrinology 102*, 1230−1236.

(22) Goetzl, E. J., An, S., and Smith, W. L. (1995) Specificity of expression and effects of eicosanoid mediators in normal physiology and human diseases. *FASEB. J. 9*, 1051−1058.

(23) Smith, W. L., Garavito, R. M., and De Witt, D. L. (1996) Prostaglandin endoperoxide H synthases (cyclooxygenases)-1 and -2. *J. Biol. Chem. 271*, 33157−33160.

(24) Rao, J. S., Lee, H. J., Rapoport, S. I., and Bazinet, R. P. (2008) Mode of action of mood stabilizers: is the arachidonic acid cascade a common target? *Mol. Psychiatry 13*, 585−596.

(25) Chang, M. C., Grange, E., Rabin, O., Bell, J. M., Allen, D. D., and Rapoport, S. I. (1996) Lithium decreases turnover of arachidonate in several brain phospholipids. *Neurosci. Lett. 220*, 171−174.

(26) Chang, M. C., and Jones, C. R. (1998) Chronic lithium treatment decreases brain phospholipase A2 activity. *Neurochem. Res. 23*, 887−892.

(27) Bosetti, F., Rintala, J., Seemann, R., Rosenberger, T. A., Contreras, M. A., Rapoport, S. I., and Chang, M. C. (2002) Chronic lithium downregulates cyclooxygenase-2 activity and prostaglandin E(2) concentration in rat brain. *Mol. Psychiatry 7*, 845−850.

(28) Basselin, M., Kim, H. W., Chen, M., Ma, K., Rapoport, S. I., Murphy, R. C., and Farias, S. E. (2010) Lithium modifies brain arachidonic and docosahexaenoic metabolism in rat lipopolysaccharide model of neuroinflammation. *J. Lipid. Res. 51*, 1049−1056.

(29) Ziboh, V. A., Miller, C. C., and Cho, Y. (2000) Metabolism of polyunsaturated fatty acids by skin epidermal enzymes: generation of antiinflammatory and antiproliferative metabolites. *Am. J. Clin. Nutr. 71*, 361S−366S.

(30) Hong, S., Gronert, K., Devchand, P. R., Moussignac, R. L., and Serhan, C. N. (2003) Novel docosatrienes and 17S-resolvins generated from docosahexaenoic acid in murine brain, human blood, and glial cells. Autacoids in anti-inflammation. *J. Biol. Chem. 278*, 14677−14687.

(31) González-Périz, A., Planagumà, A., Gronert, K., Miquel, R., López-Parra, M., Titos, E., Horrillo, R., Ferré, N., Deulofeu, R., Arroyo, V., Rodés, J., and Clària, J. (2006) Docosahexaenoic acid (DHA) blunts liver injury by conversion to protective lipid mediators: protectin D1 and 17S-hydroxy-DHA. *FASEB. J. 20*, 2537−2539.

(32) Weylandt, K. H., Krause, L. F., Gomolka, B., Chiu, C. Y., Bilal, S., Nadolny, A., Waechter, S. F., Fischer, A., Rothe, M., and Kang, J. X. (2011) Suppressed liver tumorigenesis in fat-1 mice with elevated omega-3 fatty acids is associated with increased omega-3 derived lipid mediators and reduced TNF-α. *Carcinogenesis 32*, 897−903.

(33) Chiu, C. Y., Gomolka, B., Dierkes, C., Huang, N. R., Schroeder, M., Purschke, M., Manstein, D., Dangi, B., and Weylandt, K. H. (2012) Omega-6 docosapentaenoic acid-derived resolvins and 17-hydroxydocosahexaenoic acid modulate macrophage function and alleviate experimental colitis. *Inflammation Res. 61*, 967−976.

(34) Nahman, S., Belmaker, R. H., and Azab, A. N. (2012) Effects of lithium on lipopolysaccharide-induced inflammation in rat primary glia cells. *Innate Immun. 18*, 447−458.

(35) Wang, H. M., Zhang, T., Li, Q., Huang, J. K., Chen, R. F., and Sun, X. J. (2013) Inhibition of glycogen synthase kinase-3β by lithium chloride suppresses 6-hydroxydopamine-induced inflammatory response in primary cultured astrocytes. *Neurochem. Int. 63*, 345−353.

(36) Chang, M. C., Contreras, M. A., Rosenberger, T. A., Rintala, J. J., Bell, J. M., and Rapoport, S. I. (2001) Chronic valproate treatment decreases the in vivo turnover of arachidonic acid in brain phospholipids: a possible common effect of mood stabilizers. *J. Neurochem. 77*, 796−803.

(37) Bazinet, R. P., Rao, J. S., Chang, L., Rapoport, S. I., and Lee, H. J. (2006) Chronic carbamazepine decreases the incorporation rate and turnover of arachidonic acid but not docosahexaenoic acid in brain

phospholipids of the unanesthetized rat: relevance to bipolar disorder. *Biol. Psychiatry 59*, 401−407.
(38) Lee, H. J., Ertley, R. N., Rapoport, S. I., Bazinet, R. P., and Rao, J. S. (2008) Chronic administration of lamotrigine downregulates COX-2 mRNA and protein in rat frontal cortex. *Neurochem. Res. 33*, 861−866.
(39) Cheon, Y., Park, J. Y., Modi, H. R., Kim, H. W., Lee, H. J., Chang, L., Rao, J. S., and Rapoport, S. I. (2011) Chronic olanzapine treatment decreases arachidonic acid turnover and prostaglandin E2 concentration in rat brain. *J. Neurochem. 119*, 364−376.
(40) Müller, N., Schwarz, M. J., Dehning, S., Douhe, A., Cerovecki, A., Goldstein.-Müller, B., Spellmann, I., Hetzel, G., Maino, K., Kleindienst, N., Möller, H. J., Arolt, V., and Riedel, M. (2006) The cyclooxygenase-2 inhibitor celecoxib has therapeutic effects in major depression: results of a double-blind, randomized, placebo controlled, add-on pilot study to reboxetine. *Mol. Psychiatry. 11*, 680−684.
(41) Nery, F. G., Monkul, E. S., Hatch, J. P., Fonseca, M., Zunta-Soares, G. B., Frey, B. N., Bowden, C. L., and Soares, J. C. (2008) Celecoxib as an adjunct in the treatment of depressive or mixed episodes of bipolar disorder: a double-blind, randomized, placebo-controlled study. *Hum. Psychopharmacol. 23*, 87−94.
(42) Voutsinos-Porche, B., Koning, E., Kaplan, H., Ferrandon, A., Guenounou, M., Nehlig, A., and Motte, J. (2004) Temporal patterns of the cerebral inflammatory response in the rat lithium-pilocarpine model of temporal lobe epilepsy. *Neurobiol. Dis. 17*, 385−402.
(43) Yuskaitis, C. J., and Jope, R. S. (2009) Glycogen synthase kinase-3 regulates microglial migration, inflammation, and inflammation-induced neurotoxicity. *Cell. Signalling 21*, 264−273.
(44) Knowles, R. G., and Moncada, S. (1994) Nitric oxide synthases in mammals. *Biochem. J. 298*, 249−258.
(45) Merrill, J. E., Murphy, S. P., Mitrovic, B., Mackenzie-Graham, A., Dopp, J. C., Ding, M., Griscavage, J., Ignarro, L. J., and Lowenstein, C. J. (1997) Inducible nitric oxide synthase and nitric oxide production by oligodendrocytes. *J. Neurosci. Res. 48*, 372−384.
(46) Moncada, S., and Bolanos, J. P. (2006) Nitric oxide, cell bioenergetics and neurodegeneration. *J. Neurochem. 97*, 1676−1689.
(47) Bagetta, G., Massoud, R., Rodinò, P., Federici, G., and Nisticò, G. (1993) Systemic administration of lithium chloride and tacrine increases nitric oxide synthase activity in the hippocampus of rats. *Eur. J. Pharmacol. 237*, 61−64.
(48) Harvey, B. H., Carstens, M. E., and Taljaard, J. J. (1994) Evidence that lithium induces a glutamatergic: nitric oxide-mediated response in rat brain. *Neurochem. Res. 19*, 469−474.
(49) Anai, H., Ueta, Y., Serino, R., Nomura, M., Nakashima, Y., and Yamashita, H. (2001) Activation of hypothalamic neuronal nitric oxide synthase in lithium-induced diabetes insipidus rats. *Psychoneuroendocrinology 26*, 109−120.
(50) Du, Q., Park, K. S., Guo, Z., He, P., Nagashima, M., Shao, L., Sahai, R., Geller, D. A., and Hussain, S. P. (2006) Regulation of human nitric oxide synthase 2 expression by Wnt beta-catenin signaling. *Cancer Res. 66*, 7024−7031.
(51) Bandino, A., Compagnone, A., Bravoco, V., Cravanzola, C., Lomartire, A., Rossetto, C., Novo, E., Cannito, S., Valfré di Bonzo, L., Zamara, E., Autelli, R., Parola, M., and Colombatto, S. (2008) Beta-catenin triggers nuclear factor kappaB-dependent up-regulation of hepatocyte inducible nitric oxide synthase. *Int. J. Biochem. Cell Biol. 40*, 1861−1871.
(52) Ghasemi, M., and Dehpour, A. R. (2011) The NMDA receptor/nitric oxide pathway: a target for the therapeutic and toxic effects of lithium. *Trends Pharmacol. Sci. 32*, 420−434.
(53) Talab, S. S., Elmi, A., Emami, H., Nezami, B. G., Assa, S., Ghasemi, M., Tavangar, S. M., and Dehpour, A. R. (2012) Protective effects of acute lithium preconditioning against renal ischemia/reperfusion injury in rat: role of nitric oxide and cyclooxygenase systems. *Eur. J. Pharmacol. 681*, 94−99.
(54) Schwabe, R. F., and Brenner, D. A. (2002) Role of glycogen synthase kinase-3 in TNF-alpha-induced NF-kappaB activation and apoptosis in hepatocytes. *Am. J. Physiol.: Gastrointest. Liver Physiol. 283*, G204−211.
(55) Wegener, G., Bandpey, Z., Heiberg, I. L., Volke, V., Trabace, L., Rosenberg, R., and Harvey, B. H. (2004) Combined chronic treatment with citalopram and lithium does not modify the regional neurochemistry of nitric oxide in rat brain. *J. Physiol. Pharmacol. 55*, 575−586.
(56) Maruta, S., Suzuki, E., Yokoyama, M., Sato, T., Inada, K., Watanabe, S., and Miyaoka, H. (2005) Effects of intraperitoneally injected lithium, imipramine and diazepam on nitrate levels in rat amygdala. *Psychiatry Clin. Neurosci. 59*, 358−361.
(57) Hashioka, S., Klegeris, A., Monji, A., Kato, T., Sawada, M., McGeer, P. L., and Kanba, S. (2007) Antidepressants inhibit interferon-gamma-induced microglial production of IL-6 and nitric oxide. *Exp. Neurol. 206*, 33−42.
(58) Bhalla, P., Singla, N., and Dhawan, D. K. (2010) Potential of lithium to reduce aluminium-induced cytotoxic effects in rat brain. *Biometals 23*, 197−206.
(59) Koriyama, Y., Nakayama, Y., Matsugo, S., Sugitani, K., Ogai, K., Takadera, T., and Kato, S. (2013) Anti-inflammatory effects of lipoic acid through inhibition of GSK-3β in lipopolysaccharide-induced BV-2 microglial cells. *Neurosci. Res. 77*, 87−96.
(60) Shintani, F., Kanba, S., Nakaki, T., Nakamura, R., Sato, K., Yagi, G., Richelson, E., Kato, R., and Asai, M. (1994) Inhibition by lithium of cyclic GMP formation without inhibition of nitric oxide generation in the mouse neuroblastoma cell (N1E-115). *Neuropsychopharmacology 11*, 119−124.
(61) Suzuki, E., Nakaki, T., Shintani, F., Kanba, S., and Miyaoka, H. (2002) Antipsychotic, antidepressant, anxiolytic, and anticonvulsant drugs induce type II nitric oxide synthase mRNA in rat brain. *Neurosci. Lett. 333*, 217−219.
(62) Luna-Medina, R., Cortes-Canteli, M., Alonso, M., Santos, A., Martínez, A., and Perez-Castillo, A. (2005) Regulation of inflammatory response in neural cells in vitro by thiadiazolidinones derivatives through peroxisome proliferator-activated receptor gamma activation. *J. Biol. Chem. 280*, 21453−21462.
(63) Kleinerman, E. S., Knowles, R. D., Blick, M. B., and Zwelling, L. A. (1989) Lithium chloride stimulates human monocytes to secrete tumor necrosis factor/cachectin. *J. Leukocyte Biol. 46*, 484−492.
(64) Merendino, R. A., Mancuso, G., Tomasello, F., Gazzara, D., Cusumano, V., Chillemi, S., Spadaro, P., and Mesiti, M. (1994) Effects of lithium carbonate on cytokine production in patients affected by breast cancer. *J. Biol. Regul. Homeostatic Agents 8*, 88−91.
(65) Victoratos, P., Yiangou, M., Avramidis, N., and Hadjipetrou, L. (1997) Regulation of cytokine gene expression by adjuvants in vivo. *Clin. Exp. Immunol. 109*, 569−578.
(66) Maes, M., Song, C., Lin, A. H., Pioli, R., Kenis, G., Kubera, M., and Bosmans, E. (1999) In vitro immunoregulatory effects of lithium in healthy volunteers. *Psychopharmacology (Berlin, Ger.). 143*, 401−407.
(67) Ballanger, F., Tenaud, I., Volteau, C., Khammari, A., and Dréno, B. (2008) Anti-inflammatory effects of lithium gluconate on keratinocytes: a possible explanation for efficiency in seborrhoeic dermatitis. *Arch. Dermatol. Res. 300*, 215−223.
(68) Guloksuz, S., Cetin, E. A., Cetin, T., Deniz, G., Oral, E. T., and Nutt, D. J. (2010) Cytokine levels in euthymic bipolar patients. *J. Affective Disord. 126*, 458−462.
(69) Liu, K. J., Lee, Y. L., Yang, Y. Y., Shih, N. Y., Ho, C. C., Wu, Y. C., Huang, T. S., Huang, M. C., Liu, H. C., Shen, W. W., and Leu, S. J. (2011) Modulation of the development of human monocyte-derived dendritic cells by lithium chloride. *J. Cell. Physiol. 226*, 424−433.
(70) Matsebatlela, T., Gallicchio, V., and Becker, R. (2012) Lithium modulates cancer cell growth, apoptosis, gene expression and cytokine production in HL-60 promyelocytic leukaemia cells and their drug-resistant sub-clones. *Biol. Trace Elem. Res. 149*, 323−330.
(71) Hull, M., Lee, E., Lee, T., Anand, N., LaLone, V., and Parameswaran, N. (2014) Lithium chloride induces TNFα in mouse macrophages via MEK-ERK-dependent pathway. *J. Cell. Biochem. 115*, 71−80.
(72) Arena, A., Capozza, A. B., Orlando, M. E., Currò, F., Losi, E., Chillemi, S., Mesiti, M., and Merendino, R. A. (1997) In vitro effects of lithium chloride on TNF alpha and IL-6 production by monocytes from breast cancer patients. *J. Chemother. 9*, 219−226.

(73) Martin, M., Rehani, K., Jope, R. S., and Michalek, S. M. (2005) Toll-like receptor-mediated cytokine production is differentially regulated by glycogen synthase kinase 3. *Nat. Immunol. 6*, 777−784.
(74) Zhang, P., Katz, J., and Michalek, S. M. (2009) Glycogen synthase kinase-3beta (GSK3beta) inhibition suppresses the inflammatory response to Francisella infection and protects against tularemia in mice. *Mol. Immunol. 46*, 677−687.
(75) Wang, Y., Huang, W. C., Wang, C. Y., Tsai, C. C., Chen, C. L., Chang, Y. T., Kai, J. I., and Lin, C. F. (2009) Inhibiting glycogen synthase kinase-3 reduces endotoxaemic acute renal failure by down-regulating inflammation and renal cell apoptosis. *Br. J. Pharmacol. 157*, 1004−1013.
(76) Daneshmand, A., Rahimian, R., Mohammadi, H., Ejtemaee-Mehr, S., Tavangar, S. M., Babaei Kelishomi, R., and Dehpour, A. R. (2009) Protective effects of lithium on acetic acid-induced colitis in rats. *Dig. Dis. Sci. 54*, 1901−1907.
(77) Park, H. J., Kim, H. J., Bae, G. S., Seo, S. W., Kim, D. Y., Jung, W. S., Kim, M. S., Song, M. Y., Kim, E. K., Kwon, K. B., Hwang, S. Y., Song, H. J., Park, C. S., Park, R. K., Chong, M. S., and Park, S. J. (2009) Selective GSK-3beta inhibitors attenuate the cisplatin-induced cytotoxicity of auditory cells. *Hear. Res. 257*, 53−62.
(78) Tan, W. F., Cao, X. Z., Wang, J. K., Lv, H. W., Wu, B. Y., and Ma, H. (2010) Protective effects of lithium treatment for spatial memory deficits induced by tau hyperphosphorylation in splenectomized rats. *Clin. Exp. Pharmacol. Physiol. 37*, 1010−1015.
(79) Al-Azemi, M., Omu, F. E., Kehinde, E. O., Anim, J. T., Oriowo, M. A., and Omu, A. E. (2010) Lithium protects against toxic effects of cadmium in the rat testes. *J. Assisted Reprod. Genet. 27*, 469−476.
(80) Coant, N., Simon-Rudler, M., Gustot, T., Fasseu, M., Gandoura, S., Ragot, K., Abdel-Razek, W., Thabut, D., Lettéron, P., Ogier-Denis, E., Ouziel, R., Devière, J., Lizard, G., Tellier, Z., Lebrec, D., and Moreau, R. (2011) Glycogen synthase kinase 3 involvement in the excessive proinflammatory response to LPS in patients with decompensated cirrhosis. *J. Hepatol. 55*, 784−793.
(81) Daneshmand, A., Mohammadi, H., Rahimian, R., Habibollahi, P., Fakhfouri, G., Talab, S. S., Mehr, S. E., and Dehpour, A. R. (2011) Chronic lithium administration ameliorates 2,4,6-trinitrobenzene sulfonic acid-induced colitis in rats; potential role for adenosine triphosphate sensitive potassium channels. *J. Gastroenterol. Hepatol. 26*, 1174−1181.
(82) Tay, T. F., Maheran, M., Too, S. L., Hasidah, M. S., Ismail, G., and Embi, N. (2012) Glycogen synthase kinase-3β inhibition improved survivability of mice infected with Burkholderia pseudomallei. *Trop. Biomed. 29*, 551−567.
(83) Green, H. F., and Nolan, Y. M. (2012) GSK-3 mediates the release of IL-1β, TNF-α and IL-10 from cortical glia. *Neurochem. Int. 61*, 666−671.
(84) Albayrak, A., Halici, Z., Polat, B., Karakus, E., Cadirci, E., Bayir, Y., Kunak, S., Karcioglu, S. S., Yigit, S., Unal, D., and Atamanalp, S. S. (2013) Protective effects of lithium: a new look at an old drug with potential antioxidative and anti-inflammatory effects in an animal model of sepsis. *Int. Immunopharmacol. 16*, 35−40.
(85) Chen, K., Wu, Y., Zhu, M., Deng, Q., Nie, X., Li, M., Wu, M., and Huang, X. (2013) Lithium chloride promotes host resistance against Pseudomonas aeruginosa keratitis. *Mol. Vision 19*, 1502−1514.
(86) Agrawal, S., Gollapudi, S., Gupta, S., and Agrawal, A. (2013) Dendritic cells from the elderly display an intrinsic defect in the production of IL-10 in response to lithium chloride. *Exp. Gerontol. 48*, 1285−1292.
(87) Kwon, Y. J., Yoon, C. H., Lee, S. W., Park, Y. B., Lee, S. K., and Park, M. C. (2013) Inhibition of glycogen synthase kinase-3β suppresses inflammatory responses in rheumatoid arthritis fibroblast-like synoviocytes and collagen-induced arthritis. *Joint Bone Spine*, DOI: 10.1016/j.jbspin.2013.09.006.
(88) Kang, K., Kim, Y. J., Kim, Y. H., Roh, J. N., Nam, J. M., Kim, P. Y., Ryu, W. S., Lee, S. H., and Yoon, B. W. (2012) Lithium pretreatment reduces brain injury after intracerebral hemorrhage in rats. *Neurol. Res. 34*, 447−454.
(89) Himmerich, H., Bartsch, S., Hamer, H., Mergl, R., Schönherr, J., Petersein, C., Munzer, A., Kirkby, K. C., Bauer, K., and Sack, U. (2013) Impact of mood stabilizers and antiepileptic drugs on cytokine production in-vitro. *J. Psychiatr. Res. 47*, 1751−1759.
(90) Kucharz, E. J., Sierakowski, S., Staite, N. D., and Goodwin, J. S. (1988) Mechanism of lithium-induced augmentation of T-cell proliferation. *Int. J. Immunopharmacol. 10*, 253−259.
(91) Zhu, Z. F., Wang, Q. G., Han, B. J., and William, C. P. (2010) Neuroprotective effect and cognitive outcome of chronic lithium on traumatic brain injury in mice. *Brain Res. Bull. 83*, 272−277.
(92) Li, H., Li, Q., Du, X., Sun, Y., Wang, X., Kroemer, G., Blomgren, K., and Zhu, C. (2011) Lithium-mediated long-term neuroprotection in neonatal rat hypoxia-ischemia is associated with antiinflammatory effects and enhanced proliferation and survival of neural stem/progenitor cells. *J. Cereb. Blood Flow Metab. 31*, 2106−2115.
(93) Zhao, L., Wang, F., Gui, B., Hua, F., and Qian, Y. (2011) Prophylactic lithium alleviates postoperative cognition impairment by phosphorylating hippocampal glycogen synthase kinase-3β (Ser9) in aged rats. *Exp. Gerontol. 46*, 1031−1036.
(94) Knijff, E. M., Breunis, M. N., Kupka, R. W., de Wit, H. J., Ruwhof, C., Akkerhuis, G. W., Nolen, W. A., and Drexhage, H. A. (2007) An imbalance in the production of IL-1beta and IL-6 by monocytes of bipolar patients: restoration by lithium treatment. *Bipolar Disord. 9*, 743−753.
(95) Kishter, S., Hoffman, F. A., and Pizzo, P. A. (1985) Production of and response to interleukin-2 by cultured T cells: effects of lithium chloride and other putative modulators. *J. Biol. Response Modif. 4*, 185−194.
(96) Sztein, M. B., Simon, G. L., Parenti, D. M., Scheib, R., Goldstein, A. L., Goodman, R., DiGioia, R., Paxton, H., Skotnicki, A. B., and Schulof, R. S. (1987) In vitro effects of thymosin and lithium on lymphoproliferative responses of normal donors and HIV seropositive male homosexuals with AIDS-related complex. *Clin. Immunol. Immunopathol. 44*, 51−62.
(97) Wilson, R., Fraser, W. D., McKillop, J. H., Smith, J., O'Reilly, D. S., and Thomson, J. A. (1989) The "in vitro" effects of lithium on the immune system. *Autoimmunity 4*, 109−114.
(98) Beyaert, R., Schulze-Osthoff, K., Van Roy, F., and Fiers, W. (1991) Lithium chloride potentiates tumor necrosis factor-induced and interleukin 1-induced cytokine and cytokine receptor expression. *Cytokine 3*, 284−291.
(99) Wu, Y. Y., and Yang, X. H. (1991) Enhancement of interleukin 2 production in human and Gibbon T cells after in vitro treatment with lithium. *Proc. Soc. Exp. Biol. Med. 198*, 620−624.
(100) Kucharz, E. J., Sierakowski, S. J., and Goodwin, J. S. (1993) Lithium in vitro enhances interleukin-2 production by T cells from patients with systemic lupus erythematosus. *Immunopharmacol. Immunotoxicol. 15*, 515−523.
(101) Rapaport, M. H., Guylai, L., and Whybrow, P. (1999) Immune parameters in rapid cycling bipolar patients before and after lithium treatment. *J. Psychiatr. Res. 33*, 335−340.
(102) Ohteki, T., Parsons, M., Zakarian, A., Jones, R. G., Nguyen, L. T., Woodgett, J. R., and Ohashi, P. S. (2000) Negative regulation of T cell proliferation and interleukin 2 production by the serine threonine kinase GSK-3. *J. Exp. Med. 192*, 99−104.
(103) Szuster-Ciesielska, A., Tustanowska-Stachura, A., Słotwińska, M., Marmurowska-Michałowska, H., and Kandefer-Szerszeń, M. (2003) In vitro immunoregulatory effects of antidepressants in healthy volunteers. *Pol. J. Pharmacol. 55*, 353−362.
(104) Rapaport, M. H., and Manji, H. K. (2001) The effects of lithium on ex vivo cytokine production. *Biol. Psychiatry 50*, 217−224.
(105) Boufidou, F., Nikolaou, C., Alevizos, B., Liappas, I. A., and Christodoulou, G. N. (2004) Cytokine production in bipolar affective disorder patients under lithium treatment. *J. Affective Disord. 82*, 309−313.
(106) De Sarno, P., Axtell, R. C., Raman, C., Roth, K. A., Alessi, D. R., and Jope, R. S. (2008) Lithium prevents and ameliorates experimental autoimmune encephalomyelitis. *J. Immunol. 181*, 338−345.

(107) Natsume, H., Tokuda, H., Adachi, S., Matsushima-Nishiwaki, R., Kato, K., Minamitani, C., Otsuka, T., and Kozawa, O. (2011) Wnt3a regulates tumor necrosis factor-α-stimulated interleukin-6 release in osteoblasts. *Mol. Cell. Endocrinol. 331*, 66−72.
(108) Beurel, E., and Jope, R. S. (2009) Glycogen synthase kinase-3 promotes the synergistic action of interferon-gamma on lipopolysaccharide-induced IL-6 production in RAW264.7 cells. *Cell. Signalling 21*, 978−985.
(109) Beurel, E., and Jope, R. S. (2009) Lipopolysaccharide-induced interleukin-6 production is controlled by glycogen synthase kinase-3 and STAT3 in the brain. *J. Neuroinflammation*, DOI: 10.1186/1742-2094-6-9.
(110) McGrath, H. E., Wade, P. M., Kister, V. K., and Quesenberry, P. J. (1992) Lithium stimulation of HPP-CFC and stromal growth factor production in murine Dexter culture. *J. Cell. Physiol. 151*, 276−286.
(111) Vandevoorde, V., Haegeman, G., and Fiers, W. (1992) TNF-mediated IL6 gene expression and cytotoxicity are co-inducible in TNF-resistant L929 cells. *FEBS Lett. 302*, 235−238.
(112) Vines, A., Cahoon, S., Goldberg, I., Saxena, U., and Pillarisetti, S. (2006) Novel anti-inflammatory role for glycogen synthase kinase-3beta in the inhibition of tumor necrosis factor-alpha- and interleukin-1beta-induced inflammatory gene expression. *J. Biol. Chem. 281*, 16985−16990.
(113) Baban, B., Liu, J. Y., and Mozaffari, M. S. (2013) Pressure overload regulates expression of cytokines, γH2AX, and growth arrest- and DNA-damage inducible protein 153 via glycogen synthase kinase-3β in ischemic-reperfused hearts. *Hypertension 61*, 95−104.
(114) Sharma, S. D. (1982−1983) Lithium modulates mitogen induced natural killer activity and interferon production. *Immunopharmacology 4*, 303−313.
(115) Rowse, A. L., Naves, R., Cashman, K. S., McGuire, D. J., Mbana, T., Raman, C., and De Sarno, P. (2012) Lithium controls central nervous system autoimmunity through modulation of IFN-γ signaling. *PLoS One 7* (12), e52658.
(116) Wang, L., Zhang, L., Zhao, X., Zhang, M., Zhao, W., and Gao, C. (2013) Lithium attenuates IFN-β production and antiviral response via inhibition of TANK-binding kinase 1 kinase activity. *J. Immunol. 191*, 4392−8398.
(117) Aschner, M. (1998) Immune and inflammatory responses in the CNS: modulation by astrocytes. *Toxicol. Lett. 102−103*, 283−287.
(118) Allen, N. J., and Barres, B. A. (2009) Neuroscience: Glia - more than just brain glue. *Nature 457*, 675−677.
(119) Kreutzberg, G. W. (1996) Microglia: a sensor for pathological events in the CNS. *Trends Neurosci. 19*, 312−318.
(120) Shemi, D., Azab, A. N., and Kaplanski, J. (2001) Time-dependent effect of LPS on PGE2 and TNF-α production by rat glial brain culture: influence of COX and cytokine inhibitors. *J. Endotoxin Res. 6*, 377−381.
(121) Rajkowska, G., Halaris, A., and Selemon, L. D. (2001) Reductions in neuronal and glial density characterize the dorsolateral prefrontal cortex in bipolar disorder. *Biol. Psychiatry 49*, 741−752.
(122) Rajkowska, G. (2002) Cell pathology in bipolar disorder. *Bipolar Disord. 4*, 105−116.
(123) Watkins, C. C., Sawa, A., and Pomper, M. G. (2014) Glia and immune cell signaling in bipolar disorder: insights from neuropharmacology and molecular imaging to clinical application. *Transl. Psychiatry 4*, e350.
(124) Cotter, D., Mackay, D., Landau, S., Kerwin, R., and Everall, I. (2001) Reduced glial cell density and neuronal size in the anterior cingulate cortex in major depressive disorder. *Arch. Gen. Psychiatry 58*, 545−553.
(125) Gilad, G. M., and Gilad, V. H. (2007) Astroglia growth retardation and increased microglia proliferation by lithium and ornithine decarboxylase inhibitor in rat cerebellar cultures: Cytotoxicity by combined lithium and polyamine inhibition. *J. Neurosci. Res. 85*, 594−601.
(126) Li, B., Gu, L., Zhang, H., Huang, J., Chen, Y., Hertz, L., and Peng, L. (2007) Up-regulation of cPLA(2) gene expression in astrocytes by all three conventional anti-bipolar drugs is drug-specific and enzyme-specific. *Psychopharmacology (Berlin, Ger.) 194*, 333−345.
(127) Su, H., Chu, T. H., and Wu, W. (2007) Lithium enhances proliferation and neuronal differentiation of neural progenitor cells in vitro and after transplantation into the adult rat spinal cord. *Exp. Neurol. 206*, 296−307.
(128) Beurel, E., and Jope, R. S. (2008) Differential regulation of STAT family members by glycogen synthase kinase-3. *J. Biol. Chem. 283*, 21934−21944.
(129) Rocha, E., Achaval, M., Santos, P., and Rodnight, R. (1998) Lithium treatment causes gliosis and modifies the morphology of hippocampal astrocytes in rats. *NeuroReport 9*, 3971−3974.
(130) Yuskaitis, C. J., Beurel, E., and Jope, R. S. (2010) Evidence of reactive astrocytes but not peripheral immune system activation in a mouse model of Fragile X syndrome. *Biochim. Biophys. Acta 1802*, 1006−1012.
(131) Azim, K., and Butt, A. M. (2011) GSK3β negatively regulates oligodendrocyte differentiation and myelination in vivo. *Glia 59*, 540−553.
(132) Yu, F., Wang, Z., Tanaka, M., Chiu, C. T., Leeds, P., Zhang, Y., and Chuang, D. M. (2012) Posttrauma cotreatment with lithium and valproate: reduction of lesion volume, attenuation of blood-brain barrier disruption, and improvement in motor coordination in mice with traumatic brain injury. *J. Neurosurg. 119*, 766−773.
(133) Gao, M., Yan, X., and Weng, H. R. (2013) Inhibition of glycogen synthase kinase 3beta activity with lithium prevents and attenuates paclitaxel-induced neuropathic pain. *Neuroscience 254*, 301−311.
(134) Davenport, C. M., Sevastou, I. G., Hooper, C., and Pocock, J. M. (2010) Inhibiting p53 pathways in microglia attenuates microglial-evoked neurotoxicity following exposure to Alzheimer peptides. *J. Neurochem. 112*, 552−563.
(135) Toledo, E. M., and Inestrosa, N. C. (2010) Activation of Wnt signaling by lithium and rosiglitazone reduced spatial memory impairment and neurodegeneration in brains of an APPswe/PSEN1DeltaE9 mouse model of Alzheimer's disease. *Mol. Psychiatry 15*, 272−285.
(136) Woodgett, J. R. (1990) Molecular cloning and expression of glycogen synthase kinase-3/factor A. *EMBO J. 9*, 2431−2438.
(137) Grimes, C. A., and Jope, R. S. (2001) The multifaceted roles of glycogen synthase kinase 3beta in cellular signaling. *Prog. Neurobiol. 65*, 391−426.
(138) Hoeflich, K. P., Luo, J., Rubie, E. A., Tsao, M. S., Jin, O., and Woodgett, J. R. (2000) Requirement for glycogen synthase kinase-3beta in cell survival and NF-kappaB activation. *Nature. 406*, 86−90.
(139) Ghosh, S., and Hayden, M. S. (2008) New regulators of NF-kappaB in inflammation. *Nat. Rev. Immunol. 8*, 837−848.
(140) Hofmann, C., Dunger, N., Schölmerich, J., Falk, W., and Obermeier, F. (2010) Glycogen synthase kinase 3-β: a master regulator of toll-like receptor-mediated chronic intestinal inflammation. *Inflammatory Bowel Dis. 16*, 1850−1858.
(141) Huang, W. C., Lin, Y. S., Wang, C. Y., Tsai, C. C., Tseng, H. C., Chen, C. L., Lu, P. J., Chen, P. S., Qian, L., Hong, J. S., and Lin, C. F. (2008) Glycogen synthase kinase-3 negatively regulates anti-inflammatory interleukin-10 for lipopolysaccharide-induced iNOS/NO biosynthesis and RANTES production in microglial cells. *Immunology. 128*, e275−286.
(142) Schotte, P., Van Loo, G., Carpentier, I., Vandenabeele, P., and Beyaert, R. (2001) Lithium sensitizes tumor cells in an NF-kappa B-independent way to caspase activation and apoptosis induced by tumor necrosis factor (TNF). Evidence for a role of the TNF receptor-associated death domain protein. *J. Biol. Chem. 276*, 25939−25945.
(143) Rao, R., Hao, C. M., and Breyer, M. D. (2004) Hypertonic stress activates glycogen synthase kinase 3beta-mediated apoptosis of renal medullary interstitial cells, suppressing an NFkappaB-driven cyclooxygenase-2-dependent survival pathway. *J. Biol. Chem. 279*, 3949−3955.