

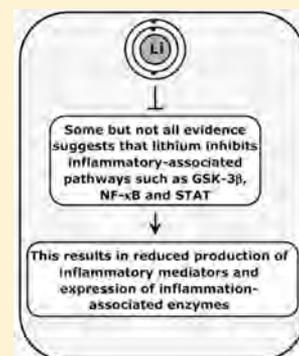
Effects of Lithium on Inflammation

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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)-1 β 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-3 β , lithium, nitric oxide, nuclear factor- κ B, 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 Cade² 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)-3 β ;^{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-1 β 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.

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For instance, they reported increased levels of IL-1 β , IL-1 receptor, myeloid differentiation factor 88, nuclear factor- κ B 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 paper¹⁴ 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-1 β 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 , Ca²⁺-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 PLA₂-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 et al.²⁷ found that chronic lithium administration decreased AA turnover, COX-2 activity and PGE₂ concentration in rat brain. Consistently, chronic lithium treatment significantly decreased lipopolysaccharide (LPS)-induced elevation in brain PGE₂ synthesis in rats.²⁸ This study²⁸ 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 PGE₂ production in rat primary glia cells.³⁴ Wang et al.³⁵ also observed that lithium significantly decreased expression of COX-2 and production of PGE₂ in primary cultured astrocytes. Similar to lithium, the mood-modulating drugs valproate,³⁶ carbamazepine,³⁷ lamotrigine,³⁸ and olanzapine³⁹ have also been found to inhibit COX-2 expression and reduce PGE₂ 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 depression⁴⁰ and bipolar disorder⁴¹ 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 Jope⁴³ observed that lithium did not alter COX-2 expression in microglia cells.

Taken together, these findings suggest that lithium attenuates COX-2 expression and PGE₂ production in 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 coauthors⁴⁷ 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 Jope⁴³ 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-1 β (IL-1 β). IL-1 β 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-1 β synthesis in human immature dendritic cells.⁶⁹ Despite these findings, most of the reviewed studies showed that lithium inhibits IL-1 β production.^{34,77,78,82,83,87,89,91–94} For example, Knijff et al.⁹⁴ observed that lithium decreased IL-1 β levels in LPS-stimulated monocytes of healthy control subjects. We found that lithium reduced LPS-induced elevation in IL-1 β secretion in rat primary glia cells.³⁴

Interleukin-2 (IL-2). IL-2 is an *anti*-inflammatory cytokine. In 1985, Kishner and co authors⁹⁵ 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, Szein 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 affect⁸⁹ 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 Jope¹⁰⁹ 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 produc-

tion,^{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 Manji¹⁰⁴ found that lithium increased IL-10 levels in whole blood cultures from normal control subjects. Nonetheless, Matsebatale 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, Sharma¹¹⁴ 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-1 α , 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-1 β , NO, PGE₂, 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- κ B in microglia cells. Moreover, Yu and coauthors¹³² 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-3 β is the one that has been repetitively reported to alter inflammatory responses of various types. Glycogen synthase kinase-3 β 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-3 β and inflammation. They found that GSK-3 β facilitates the activity of the transcription factor nuclear factor (NF)- κ B resulting in an enhanced inflammation in mice.¹³⁸ Nuclear factor- κ B 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-3 β 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-workers⁷³ found that GSK-3 β 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-3 β attenuated NF- κ B activity and decreased the production of pro-inflammatory mediators in mice. Similarly, Zhang et al.⁷⁴ observed that lithium inhibition of GSK-3 β decreased LPS-induced mortality, TNF- α secretion, and NF- κ B activation in mice. Wang et al.³⁵ showed that inhibition of GSK-3 β and NF- κ B 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-3 β (inhibition)-associated anti-inflammatory effects of lithium are not solely due to inactivation of NF- κ B.^{69,71,108,109,115,116,141} Another downstream target of GSK-3 β is the transcription factor signal transducer and activator of transcription (STAT). It was found that inhibition of GSK-3 β 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-3 β attenuates NF- κ B 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-3 β enhanced NF- κ B activity and the increased expression of COX-2.

Overall, the summarized data suggest that GSK-3 β 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.

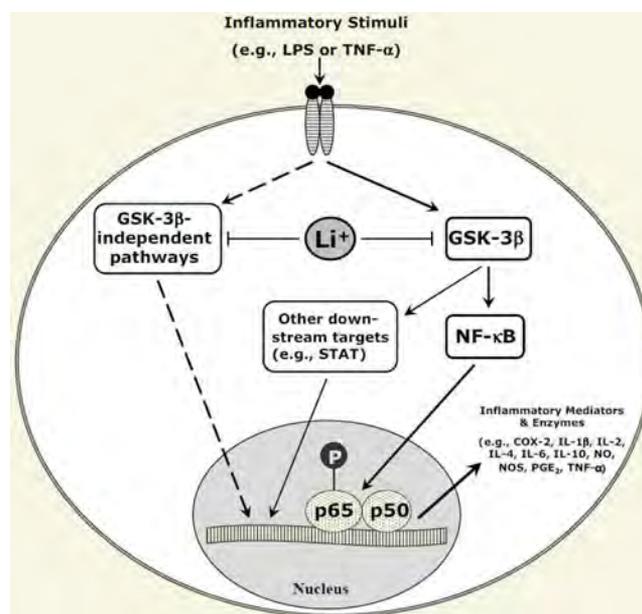


Figure 1. Simplified model illustrating the association between lithium and inflammation. Lithium inhibits GSK-3 β , resulting in decreased NF- κ B activity. The reduction in NF- κ B activity (translocation of p65–p50 to the nucleus and stimulation of its transcriptional activity) leads to attenuated expression of inflammatory-associated mediators and enzymes. Inhibition of GSK-3 β by lithium affects other downstream effectors (of GSK-3 β) such as STAT, which also results in suppression of inflammation. In addition, lithium alters the inflammatory response through GSK-3 β -independent mechanisms. See text for references. Abbreviations: COX-2, cyclooxygenase-2; GSK-3 β , glycogen synthase kinase-3 β ; IL, interleukin; Li, lithium; LPS, lipopolysaccharide; NF- κ B, nuclear factor- κ B; NO, nitric oxide; NOS, nitric oxide synthase; PGE₂, prostaglandin E₂; 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.

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