Review

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Review

The Mechanisms of Lithium Action: The Old and New Findings

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Abstract: Despite lithium's presence in modern psychiatry for three quarters of a century, the mechanisms of its therapeutic action have not been fully elucidated. In the article, the evolution of the views on these mechanisms is presented, and both the old and new findings are discussed. Among the old mechanisms, lithium effect on the purinergic system, electrolyte metabolism and membrane transport, second messenger systems: cyclic nucleotide and phosphatidylinositol (PI), glycogen synthase kinase-3beta (GSK-3β), brain-derived neurotrophic factor, and neurotransmitters, are discussed. The new data have been obtained from in vitro studies, molecular biology and genetic researches. They also showed the effect of lithium on the immune system, biological rhythms, and telomere functions. In the article, each lithium mechanism is considered in the light of its association with the pathogenesis of bipolar disorder or/and as a marker of lithium response. This review, although not complete, shows that the possible mechanisms of lithium action are multifold. It turned out that many apparent "old" mechanisms had their revival in research performed in the 21st century. Additionally, many studies eventually converged on the mechanisms postulated in the 1980s/1990s of inhibiting GSK-3β and PI by lithium.

Keywords: lithium; bipolar disorder; lithium response

1. Introduction

In 2024, the 75th anniversary of introducing lithium into contemporary psychiatry is observed. This event was attested by an Australian psychiatrist, John Cade's article, in the 1949 issue of the Medical Journal of Australia [1]. In 1963, the first observations appeared pointing to lithium's property to prevent the recurrences of mood disorders [2]. As a consequence of the latter, nowadays, lithium is the first choice drug for preventing recurrences in mood disorders, mainly bipolar disorder (BD), recommended in all major guidelines [3]. In treating an acute episode, lithium possesses strong antimanic and moderate antidepressant activity but is especially useful for the augmentation of antidepressant medications in treatment-resistant depression [4]. It was also demonstrated that lithium administration exerts a suicide-preventive, immunomodulatory and anti-dementia effects [5,6].

However, despite the three quarters of a century's presence of lithium in modern psychiatry, the mechanisms of its therapeutic action have still not been fully elucidated. In the paper, we show the evolution of the views on these multiple mechanisms, discussing both the old and new findings, and we show a few investigators' instrumental role in some discoveries. Each mechanism will be considered in light of its association with the pathogenesis of BD or/and as a marker of lithium response.

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2. Old Findings

2.1. Uric Acid and Purinergic System

2.1.1. Uric Acid

The effect of lithium on uric acid which constitutes an important element of the purinergic system can be considered as the oldest proposed mechanism of lithium's therapeutic action [7]. The first medical application of lithium was performed in 1859 by Alfred Garrod (1819-1907) in the treatment of gout [8]. The rationale for using lithium, was the previous observation of increased urate levels in patients with gout and the good solubility of the lithium urate. Therefore, lithium was meant to eliminate the urates as lithium urate [8]. In the same vein, in 1886, the Danish scientist Carl Lange (1834-1900) suggested the uric acid diathesis as a pathogenic mechanism of periodical depression and proposed the therapeutic use of lithium carbonate as a treatment method allegedly normalizing the uric acid levels [9].

The concept of the pathogenic role of uric acid concerning mood disorders and lithium treatment also made a basis for introduction of lithium to contemporary psychiatry by John Cade (1912-1980) who observed that urine of manic patients was particularly toxic to guinea pigs. Cade attributed this to the excess of urates and administered lithium urate to the animals obtaining a sedative effect, and subsequently lithium carbonate with the same result. This prompted him to treat manic patients with lithium carbonate with spectacular outcomes [1].

The observations of uric acid alterations in mood disorders might indicate the involvement of this substance in the pathogenesis of mood disorders and the effect of lithium. In 1968, it was shown that lithium had uricosuric effect in patients with BD and its excretion increases in the early phase of remission [10]. Whereas the 21st century brought further indications of uric acid in the pathogenesis of bipolar disorder. The Taiwanese researchers have shown that 16.4% of patients with bipolar disorder and 13.6% of the control group had gout. The risk of onset of gout during the 6-year observation period was 1.19 times greater for people with this disease as compared to the control group [11]. Clinical studies revealed that patients with the first episode of mania had increased concentrations of uric acid, which decreased as the clinical condition improved after one month of treatment [12,13]. A meta-analysis conducted by Italian authors has shown that patients with BD have significantly higher serum concentrations of uric acid as compared to healthy individuals and those suffering from periodic depression [14]. In lithium-treated patients, it was also shown that serum lithium levels positively correlated with those of uric acid [15].

2.1.2. Purinergic System

Lithium might also influence the purinergic signaling system. The concept of this system was proposed in the 1970s by Geoffrey Burnstock (1929-2020) and defined purine nucleotides: adenosine 5′-triphosphate (ATP) and adenosine diphosphate (ADP) as extracellular messengers [16].

Brazilian authors showed that in patients with BD, adenosine concentration is lower than in the control group and there is a negative correlation between adenosine concentration and depression severity [17]. An experimental study has also found that lithium increases adenosine concentration by inhibiting ectonucleotidase [18].

The role of the purinergic P2X7 receptor in the pathogenesis of BD has been postulated. This receptor mediates the processes of apoptosis, proliferation, and release of proinflammatory cytokines, as well as the mechanisms of neurotransmission and neuromodulation [19]. The P2X7 receptor gene is located on chromosome 12q23-24, which is described as a potential *locus* for BD. An association between the P2RX7 gene polymorphism of this receptor and a predisposition to BD has been found [20].

Lithium's effect on purinergic signaling can be connected with the neuroprotective effect on the drug. Chronic lithium treatment inhibits ATP-induced cellular death by decreasing the ATP and increasing adenosine levels [18]. The neuronal and microglial cells are responsive to in vitro ATP treatment leading to ATP-mediated neural cell death and microglia phenotype responding to

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inflammatory state. Lithium treatment resulted in the modulation of neuronal cell response, by preventing cell death, however, was unable to prevent the microglia inflammatory response. This led to the conclusion that the purinergic-based mechanism of lithium action occurs more likely in neurons [21].

2.2. Electrolyte Metabolism and Membrane Transport

Lithium is a monovalent cation, belonging to the first group of the Mendeleev table, along with sodium and potassium. In the 1960/70s, interest was kindled in the possible effect of lithium on electrolyte metabolism and transmembrane transport in relation to its therapeutic mechanisms.

2.2.1. Lithium Accumulation in the Organism

An Australian psychiatrist, Maurice Serry, hypothesized that the therapeutic response to lithium can be proportional to the amount of the retention of the ion in the organism. He elaborated on the lithium excretion test measuring the excretion of lithium within 4 hours after loading a dose of 1200 mg of lithium carbonate [22]. He found that manic patients who were lithium retainers responded to lithium favorably while the subjects excessively excreting lithium did not [23]. It is considerable that the higher retention of lithium could be related to a decreased elimination of lithium from the cells which is a topic of the next subchapter.

2.2.2. Transmembrane Lithium Transport

In 1975, it was found that the main mechanism of transporting lithium out of the cells is the lithium-sodium counter-transport system (LSC). The discovery was made on red blood cells by a team at Harvard Medical School led by Daniel Tosteson (1925-2009) who was the dean of the school from 1977 to 1997 [24]. Since the LSC is a factor determining lithium concentration in cells, e.g., in erythrocytes, its activity is related to the red blood cell lithium ratio. This index was further widely investigated concerning the pathogenesis of BD and therapeutic aspects of lithium treatment. A higher lithium blood cell index determines the ratio of lithium concentration in cells to that in serum. In patients with bipolar affective disorder, a higher concentration of lithium in the red blood cell was found, in comparison with healthy subjects. This could indicate a reduced efflux of lithium from the blood cells governed by LSC [25,26]. In other studies, the genetic component of lithium ratio was established [27] and a lower rate of lithium transport from the cells in bipolar patients compared with control subjects was confirmed [28]. However, the potential of the LSC mechanism for the pathogenesis of BD as well as the quality of lithium response has not been investigated in subsequent decades.

2.2.3. Sodium-Potassium ATPase

In the 1970/80s, the findings of decreased activity of sodium-potassium-activated adenosine triphosphate pump (sodium-potassium ATPase) in erythrocytes of mood disorder patients were reported as well as the increased activity of this pump resulting from lithium administration [29–32]. The sodium-potasiom ATPase hypothesis for BD was formulated by El-Mallakh and Wyatt in 1995 [33]. This concept was further confirmed in molecular genetic studies [34,35]. Therefore, the mechanism of lithium action in this respect could relate to the pathogenesis of bipolar illness. Unfortunately, the studies on lithium effect on Na, K-ATPase have been not performed in recent decades.

2.3. Second Messenger Systems

Second messenger systems modulate physiological processes by transmitting the signals from cell-surface receptors (first messengers) to the intracellular effectors – enzymes, ion channels, and transporters. There are two major classes: cyclic nucleotide and phosphatidylinositol (PI) systems [36]. They both transpired to be connected with the pathogenesis of BD or/and lithium mechanisms.

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2.3.1. Cyclic Nucleotide System

A synthesis of messenger cyclic monophosphate adenosine (cAMP) as a result of epinephrine-caused adenylyl cyclase stimulation was described by Earl Sutherland (1915-1974), a Nobel laureate in medicine in 1971 [37]. Further studies showed that G-protein subunits work as signal transducers between receptors and adenylate cyclase [38]. Israeli researchers led by Robert Haim Belmaker showed that lithium treatment inhibits the adenyl cyclase activity and reduces the cAMP accumulation in the brain [39]. Chronic lithium treatment was also shown to interfere with the dissociation of G-protein subunit Gi [40]. The study by Harvey et al. [41] showed that chronic lithium treatment resulted in decreased cAMP levels caused by increased activity of cAMP-phosphodiesterase and increased cGMP levels in rat's cortical regions.

In recent decades, evidence for the pathogenic role of adenylate cyclase in BD and in the therapeutic mechanism of lithium has been collected. In 2009, it was shown that lithium and carbamazepine preferentially inhibit specific isoforms – AC5 which might be connected to their antidepressant effect [42]. The genome-wide association study (GWAS) in 2014 revealed the adenylate cyclase-2 gene (*ADCY2*) as a risk gene for BD [43]. In 2020, Iranian researchers confirmed the association of the *ADCY2* polymorphism with BD and suggested it as a predictive marker of lithium response [44].

2.3.2. Phosphatidylinositol System

The PI system is crucial for receptor-mediated signal transduction, involving the hydrolysis of phosphoinositides and the release of inositol trisphosphate (IP3) as a second messenger. The lithium effect on the PI system resulting in the inhibition of inositol monophosphatase (IMPase) was first demonstrated by American researchers from St Louis, Loretta Hallcher and William Sherman, in 1980 [45]. In 1989, the British physiologist and biochemist, Michael Berridge (1938-2020) described the role of inositol trisphosphate (IP3) in cell signaling and calcium regulation [46]. He also suggested the uncompetitive inhibitory mechanism of lithium on inositol phosphate metabolism, and formulated an inositol depletion hypothesis of BD. According to that hypothesis, lithium influences the PI system by weakening the signaling. The proposed lithium mode of action includes uncompetitive inhibition of the IMPase which causes increased inositol-1-monophosphate (I1P) levels, followed by phosphoinositols accumulation, decreased phosphatidylinositol concentration, and altered levels of key membrane phospholipids [46].

Lithium also lowers the phosphatidylinositol/phosphatidylcholine ratio in cell membranes [47],decreases the amount of phosphatidylinositol-4,5-bisphosphate (PIP2) levels in the BD patient's platelet membrane and reduces the phosphatidylinositol-specific phospholipase C (PIPLC) which is important for the generation of IP3, diacylglycerol and also cAMP, resulting in down-regulation of inositol phosphates [48,49]. Israeli authors have performed experimental studies on mice, depriving them of one of the two genes associated with the PI system: *IMPA1* (inositol monophosphatase-1) and *SMIT1* (sodium myo-inositol transporter-1). It turned out that both genetic knock-out procedures caused behavior resembling the effect after lithium administration. This may indicate that both inositol depletion and accumulation of phosphoinositols play a role in the effects caused by lithium [50].

The molecular-genetic studies of the 21st century can point to a role of the PI system in the pathogenesis of BD. A GWAS of BD performed in 2008 showed an association with the diacylglycerol kinase eTa (*DGKH*) gene which encodes a key protein in the PI pathway [51]. In 2010, an association between polymorphism in the *IMPA2* gene and BD was found [52].

2.4. Glycogen Synthase Kinase-3 (GSK3) Activity

Glycogen synthase kinase-3 (GSK3) is a serine/threonine kinase existing in two isoforms: GSK3 alpha (GSK3α) and GSK3 beta (GSK3β). It is involved in numerous signaling pathways with over a

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hundred known substrates and multiple physiological functions. The GSK3β is connected, among others, with neurogenesis, neuronal polarization, axon growth, and biological rhythms [53].

The GSK3β is one of the best-described molecular targets of lithium. In 1996, two independent studies by Peter Klein and Douglas Melton from the University of Pennsylvania [54] and Vuk Stambolic et al. from the University of Toronto [55]presented the direct mechanism of GSK3β inhibition. Also the indirect way of lithium caused inhibition was described involving the phosphorylation of N-terminal serines of both GSK3*α* and GSK3β.

In a recent review, the four most important substrates of GSK3β were indicated that may contribute to lithium effects in BD. They include the transcription factor cAMP response element-binding protein (CREB), the RNA-binding protein FXR1 (Fragile X related protein 1), kinesin subunits, and the cytoskeletal regulator CRMP2 (Collapsin response mediator protein 2). All these substrates are in different ways associated with the pathogenesis of BD [56]. Lithium's inhibition of GSK3β influences also the PI3K/Akt pathway which leads to increased Akt-1 activity by inhibiting phosphoinositide 3-kinase-mediated Akt phosphorylation [57].

In the next subchapters, it will be shown how many mechanisms of lithium can be eventually related to the inhibition of GSK3β. However, given the multiple substrates of this enzyme, it is hard to say which of them is most important to the therapeutic effect of the drug in BD. In a recent GWAS study involving 40,000 BD subjects no common variants of the *GSK3β* gene were associated with an increased risk for BD [58]. Whereas, it was found that the lithium effect on GSK3β might play a role in lithium-induced renal decline [59] or in the anti-suicidal properties of this ion [60].

2.5. Brain-Derived Neurotrophic Factor

The brain-derived neurotrophic factor (BDNF) was identified in 1982 and was quickly proved to be the most explored neurotrophin in studies on the pathogenesis and treatment of mental disorders [61]. BDNF is essential for the function and survival of neurons and modulates the activity of such neurotransmitters as glutamate, gamma-aminobutyric acid, dopamine, and serotonin. The BDNF system is significant in the pathogenesis and treatment of mood disorders [62]. The Val66Met polymorphism of the *BDNF* gene is linked to a predisposition to BD in the European population [63].

Experimental studies have shown that lithium increases the expression of BDNF in the rat brain. One of the mechanisms for increasing BDNF expression by lithium is the activation of CREB, which stimulates the transcription of the *BDNF* gene [64]. Clinical studies have shown that BDNF serum concentrations are reduced during episodes of both mania and depression and increase after successful pharmacological treatment, including lithium. A low concentration of BDNF is considered a marker of late-stage bipolar affective disorder [65]. However, we found that in excellent lithium responders despite of long duration of BD (20 years or more) serum BDNF was not different from healthy subjects [66]. We demonstrated that, in patients with BD, the Val allele of the Val66Met polymorphism, determines better cognitive functions associated with prefrontal cortex activity. This relationship was specific to BD and did not occur in schizophrenic patients or healthy people [67]. We also showed that the prophylactic effect of lithium is connected to the Val66Met polymorphism of the *BDNF* gene [68]

2.6. Neurotransmitters

Since the 1960s, neurotransmitters such as catecholamines (norepinephrine, dopamine) and serotonin have been implicated in the pathogenesis of mood disorders, and in the therapeutic mechanism of antipsychotic and antidepressant drugs [69–71]. The effect of lithium on these neurotransmitters was also investigated.

2.6.1. Dopamine

A recent version of the dopamine hypothesis of BD was presented in 2017 [72]. Hyperdopaminergia (elevations in D2/D3 receptor availability) was proposed to underlie mania,

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while increased dopamine transporter (DAT) would lead to reduced dopaminergic function and depression. Since the 1970s, there has been evidence that lithium reduces dopaminergic activity which may be connected with its antimanic effect [73]. Can et al. [74] showed that chronic lithium treatment rectifies maladaptive dopamine release in the nucleus accumbens. More recent reviews point to regulation by lithium of dopamine transmission and the relationship of this effect to GSK3β [75,76].

2.6.2. Serotonin

A hypothesis on the mechanism of long-term lithium action by stimulating serotonergic neurotransmission was proposed forty years ago [77]. The review of Price et al. [78] suggested that lithium's primary action on the serotonergic system may be presynaptic with many postsynaptic effects resulting in enhancing effect on this neurotransmission. Recently, a study using positron emission tomography (PET) was made in patients with a depressive episode in the course of BD. It was found that the beneficial effect of lithium was associated with weaker binding of both the serotonin transporter and the 5-HT1A receptor before treatment [79]

3. New Findings

3.1. In Vitro Studies

Research on lithium's mechanisms in recent years applied the novel in vitro methods using the peripheral blood mononuclear cells (PBMCs), lymphoblastoid cell lines (LCLs), and induced pluripotent stem cells (iPSC). In most studies, the characteristics of cells obtained from so-called "lithium responders" (LR) and "lithium non-responders" (LNR) were compared.

3.1.1. Peripheral Blood Mononuclear Cells (PBMCs)

The study of human PBMCs from BD patients confirmed that lithium treatment results in the GSK-3β phosphorylation in Ser9 which can be evaluated as a biochemical marker of therapeutic response to the drug [80]. It was also shown that PBMCs from BD patients and controls differ in immunophenotypes, showing immunologic imbalance in BD. The in vitro lithium treatment of PBMCs resulted in increased percentage of CD14+ monocytes [81].

3.1.2. Lymphoblastoid Cell Lines (LCLs)

Lymphoblastoid cell lines (LCLs) are cell lines derived from B lymphocytes, typically immortalized using the Epstein-Barr virus (EBV) [82]. It was found that lithium did not alter the gene expression in LCLs of healthy subjects, but significantly those in BD patients – mostly the genes involved in apoptosis [83]. In an LCLs-based genome-wide expression study, 2060 genes differentially expressed between LR and LNR after in vitro lithium treatment. The pathways analysis and qPCR validation showed insulin-like growth factor 1 as a significant biomarker of lithium response [84]. Other study showed that lithium treatment of LCLs from LR restored the cell viability and influenced the GSK-3β expression [85]. Comparing the RNA of LCLs obtained from women with BD, a higher expression of the *HDGFRP3* (hepatoma-derived growth factor-related protein-3) and *ID2* (Inhibitor of DNA binding 2) genes was found in LR. Both genes are associated with neurogenesis, and the former has neurotrophic properties [86]. The differences in immunoglobulin-related genes between LCLs from patients with BD and healthy individuals were found as well as between LR and LNR [87].

Lithium in vitro treatment's effect on microRNA (miRNA) expression identified seven miRNAs significantly changed after four days and four changed after 16-day treatment, suggesting miRNAs as candidate's biomarker of lithium treatment [88]. In other study, the differences in 335 mRNA and 77 miRNA between LR and LNR, mainly related to immune processes, were identified, suggesting lithium's anti-inflammatory effects [89].

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3.1.3. Pluripotent Stem Cells

Pluripotent stem cells (PSCs) are a type of cells characterized by the ability to self-renew and differentiate into any type of cells found derived from the inner cell mass of embryos, primordial germ cells, teratocarcinoma or male germ cells [90]. The studies of iPSC neurons derived from BD patients showed reversed hyperexcitability after the treatment only in neurons from LR [91,92]. The cortical spheroids, or brain-like tissues derived from iPSCs of BD patients, showed smaller size and lower excitability of the neurons compared to control individuals. Adding lithium restored the excitability of neurons to levels seen in control individuals [93]. The mechanism of restoring neuronal hyperactivity in LR was associated with changes in sodium currents and the Akt signaling pathway, related to protein kinases B, which determine cell growth and proliferation [94]. Neuronal progenitor cells derived from iPSCs and obtained from LR showed increased resistance to the toxic effects of methamphetamine [95]. Using the same model, a reduced expression of the *LEF1* gene (lymphoid enhancer-binding factor 1), which regulates neuronal activity, was demonstrated in LNR [96]. A study of cortical neurons derived from iPSCs confirmed the significance of the phosphatidylinositol (PI) system in the mechanism of lithium action. Lithium's inhibition of the IMPA1 enzyme, a key component of the PI system, was associated with reduced neuronal excitability and calcium ion release [97].

3.2. Biological Rhythms

Circadian rhythms are intrinsic, 24-hour cycles regulating various physiological processes including sleep-wake cycle, body temperature regulation, and hormone secretion, driven by molecular clocks and synchronized with the external environment, primarily through light-dark cycles [98]. They are regulated by clock genes constituting feedback loops of transcription and translation. The positive feedback loop includes the aryl hydrocarbon receptor nuclear translocator-like (ARNTL) (also known as BMAL1) and circadian locomotor output cycles kaput (CLOCK). The CLOCK-BMAL1 complexes activates expression of nuclear receptors REV-ERBα and RORα and several clock genes such as period (PER1/PER2) and cryptochrome (CRY1/CRY2) [99]. The animal model of bipolar mania bases on ClockΔ19 mice with disrupted molecular circadian clock [100]. The disturbance of biological rhythms in BD is well-documented, with most studies indicating a predominance of eveningness chronotype in these patients [101].

The results from 95 studies showed that lithium delays the phase in various circadian rhythms (sleep-wakefulness cycles, activity rhythms and peaks in elevation of body temperature), and also lengthens the circadian period [102]. Studies using skin fibroblast models indicated that LR tend to have a higher level of morningness chronotype [103], and lithium treatment normalizes circadian rhythm disturbances [104]. This aligns with findings from Poznań and Kraków centers, where BD patients on lithium showed a tendency towards a morningness chronotype [105]. Recently, Mishra et al. [106] demonstrated differences in the expression of circadian clock genes between BD patients and healthy individuals, as well as between patients with different lithium responses (LR vs. LNR) using a fibroblast model. The most significant differences involved the *Per 1* (clock protein PERIOD 1) and *Per 3* genes. In our own study, the association with the degree of lithium prophylaxis was found for six SNPs (single nucleotide polymorphisms) and three haplotype blocks of *ARNTL* gene and two SNPs and one haplotype block of the *TIM* (timeless) gene [107].

The nuclear receptor REV-ERBα was shown as a potential target for GSK3β and lithium [108]. In the study of mice, lithium treated tissue slices and cells showed elongation of period locomotor activity rhythms, lengthening the molecular oscillations in the suprachiasmatic nucleus, lung tissue and fibroblasts, and elevated *Per2* expression. The described effects might be caused by the lithium effect on the GSK3β [109].

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3.3. Telomere Functions

The ends of chromosomes are protected by the protective cap. That structure was named *telomere* (from the Greek words *telos* – end, and *meros* – part) and the protective function is *telomere capping*. The 2009 Nobel Prize winners Elizabeth Blackburn, Carol Greider, and Jack Szostak explained the nature of telomeres and showed the mechanism behind chromosomes protection by telomeres and the role of telomerase [110].

Telomere length is considered a marker of aging processes. GWAS studies have shown the genetic determination of this phenomenon, with the most significant influence of the leucine-rich repeat gene (*LRRC34*) [111]. Several studies indicated shorter telomeres in BD patients and/or the restoration of their normal length with lithium treatment [112–114]. It was shown that the duration of lithium treatment is positively associated with leukocyte telomeres length in BD patients [115] and correlates with the expression of the telomerase reverse transcriptase (TERT) enzyme [116]. However, the latest study involving 591 patients on lithium did not show a correlation between the duration of lithium use and aging markers, including telomere length [117].

The study on an animal model of depression showed that the lithium naïve Flinders Sensitive Line rats presented shorter telomere length, downregulated telomerase reverse transcriptase expression, and had reduced telomerase activity. Lithium treatment resulted in restored telomerase activity, and normalized telomerase reverse transcriptase expression in the rat's hippocampus. This might mean a protective effect against telomere shortening and suggests the neuroprotective role of lithium [118].

3.4. Immunomodulatory Effects

The long-known effect of lithium treatment is its induction of granulopoiesis in the bone marrow by increasing the granulocyte colony-stimulating factor [119,120]. The studies in recent years, highlighted the immunomodulatory effect of lithium in the context of low-grade chronic inflammation and microglial hypothesis of BD [121].

In a review by Sakrajda & Szczepankiewicz [122] the evidence is presented for lithium's reduction of pro-inflammatory cytokines i.e., Interleukin (IL)-1β, Interferon (IFN)-γ, Tumor Necrosis Factor (TNF), IL-6, and Monocyte Chemoattractant Protein (MCP)-1 expression as well as elevated expression of anti-inflammatory cytokine IL-10. The lithium action on the inflammatory system might be related to lithium inhibition of GSK-3β. The GSK-3β activation is an important regulative mechanism of the NOD-like receptor protein 3 (NLRP3) inflammasome activation, affecting the production of the inflammatory cytokines [123]. Recently, we showed that mood-stabilizing treatment (with lithium or other drug) of BD patients influences the inflammasome-regulated cytokines but only lithium-treated patients presented elevated expression of IL-10 [124]. Using the more simplistic in vitro model of neuroinflammation with the microglia cell line (HMC3) and focusing on NLRP3 inflammasome we showed that lithium treatment (with concentration similar to those observed in the brains) of microglia induced with innate-immune cytokines caused significant anti-inflammatory effect affecting NLRP3 inflammasome priming, activation, and IL-1β protein expression [125].

3.5. Antiviral Effects

The lithium immune-related mechanism also includes its antiviral actions. The first description was made by Julian Lieb in 1979, presenting two patients with recurrent herpes virus infection obtaining remission during lithium treatment [126]. One year later, researchers from the University of Birmingham using a hamster kidney model, demonstrated lithium's inhibition of herpes simplex virus (HSV) [127].

Retrospective research of labial herpes in patients receiving prophylactic lithium for was carried out within a collaborative study of the Department of Adult Psychiatry, Poznan University of Medical Sciences, and the Department of Psychiatry of the University of Pennsylvania. In the Polish

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sample, during lithium therapy, the full cessation of herpes recurrences occurred in 46% patients with labial herpes and the general decrease in recurrence frequency was 64%. The better effect was observed in patients in whom serum lithium concentration was higher than 0.65 mmol/l, and intracellular (erythrocyte) lithium concentration exceeded 0.35 mmol/l. In the group of American BD patients treated with lithium, the frequency of labial herpes recurrences in comparison with the five years before the treatment decreased by 73%. In patients with recurrent depression receiving antidepressant drugs, no significant difference was observed [128].

The anti-herpes effect of lithium could be related to its prophylactic and therapeutic effect in dementia as the infection with herpes simplex virus type 1 (HSV1) makes a significant risk factor for Alzheimer's Disease [129].

The studies of lithium effect on the RNA viruses pertained mostly to respiratory infections. Amsterdam et al. [130] in a retrospective study showed a significant reduction in mean yearly rates of flu-like infections in lithium- but not antidepressant-treated patients. Landen et al. [131] demonstrated a 28% decrease in respiratory infections, part of which is likely due to the RNA viruses, during chronic lithium administration.

Shortly after the outbreak of the COVID-19 epidemic, a paper reviewed the antiviral effect of lithium on coronaviruses in animals [132]. A hope was expressed that the drug can be useful for patients with COVID-19 [133]. However, there is only one randomized clinical trial showing that adding lithium reduces the severity of the COVID-19 infection [134]. Whereas, the review of electronic records of 26,554 patients demonstrated that the incidence of infection was lower in those with lithium levels within therapeutic limits (0.5–1.0 mmol/L) compared with those with lithium levels >0.5 mmol/L [135].

3.6. Genetic Studies

In the 21st century, research have arisen seeking genetic underpinnings of lithium' therapeutic mechanism and efficacy, using various methodologies. Lithium response was mostly measured by the Retrospective Assessment of the Lithium Response Phenotype Scale known as the Alda Scale [136].

3.6.1. Candidate Genes

In 2013, the review of candidate genes connected with lithium's prophylactic response appeared, written by one of the authors of this review [137]. Since then, there were some additions, also performed in the Poznań center, e.g., showing the association of lithium efficacy with genes of the stress response [138]. In 2021, Senner et al. [139], among candidate genes showing association with lithium efficacy at least in two studies listed six genes such as *GSK3β, BDNF*, serotonin transporter *(5HTTLPR),* calcium voltage-gated channel auxiliary subunit gamma 2 *(CACNG2*), nuclear receptor subfamily 1 group D member 1 *(NR1D1),* and dopamine receptor D1 *(DRD1)* gene.

3.6.2. Genome-Wide Association Studies (GWAS)

The first GWAS of lithium response in patients with BD was performed by Perlis et al. in 2009 [140]. They assessed the five-year risk of recurrence in 1177 BD patients, including 458 treated with lithium. Comparing LR with healthy controls, the difference was found in the *GRIA2* gene, coding ionotropic AMPA glutamatergic receptor. In 2014, Chen et al. [141]on the population with Han Chinese ancestry demonstrated the association of lithium response with the gene encoding glutamate decarboxylase-like protein 1 *(GADL1).* Two years later, Song et al. [142] on a sample of 3874 lithium users from Sweden and the UK showed an association between lithium response with the SEC14 and spectrin domains 1 (*SESTD1*) gene encoding a synapse protein that directly binds to phospholipids. Recently, Wolter et al. [143]conducted a GWAS study to identify a region on the genome associated with lithium-induced proliferation of neuronal progenitor cells. They found that this region is located

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on chromosome 3, p21.1, with the gene *GNL3* (G protein nucleolar 3) being the most significant for lithium's activity.

3.6.3. ConLiGen Project

In 2009, the Consortium of Lithium Genetics (ConLiGen) was founded as a joint initiative of the International Group for Study of Lithium-treated Patients (IGSLI) and the National Institute of Mental Health. The initial report about this event was published in 2010 [144]. The first results of the GWAS appeared in 2016, focusing on the molecular-genetic aspects of lithium's prophylactic efficacy in BD. The study involved 2,563 patients from 22 participating centers. A region on chromosome 21, containing four SNPs was found to be associated with lithium efficacy. This sector incorporates two long non-coding RNAs (lncRNAs) that regulate gene expression in the central nervous system [145]. In the next years, the ConLiGen group evaluated, among others, the connection between preventing recurrences in BD, and the polygenic risk score (PRS) for varied conditions. The PRS for schizophrenia correlated with worse lithium prophylaxis [146]. This corresponded with our study showing a negative association between the prophylactic efficacy of lithium and a tendency to psychotic symptoms [147]. It was found that PRS for major depressive disorder was also negatively associated with such efficacy of lithium [148]. In another research, the PRS for attention deficit hyperactivity disorder (ADHD) correlated with a poorer prophylactic effect of lithium, and a PRS for schizophrenia with worse adherence to treatment [149]. Worse response to lithium was also associated with higher PRS for diabetes and hypertension in bipolar 1 but not bipolar 2 patients [150].

The ConLiGen group also examined the association of lithium's prophylactic efficacy with human leukocyte antigen (HLA) genes. They found that a good response to lithium was associated with HLA genes linked to lower inflammation, whereas a poorer response was associated with HLA genes linked to higher inflammation [151]. In another study, 36 candidate genes associated with a good prophylactic response to lithium were identified, primarily involving the cholinergic and glutamatergic systems [152]. Recently, a collaborative study between ConLiGen and the Pharmacogenomics of Bipolar Disorder group found a link between lithium's prophylactic efficacy and the function of focal adhesions, important for neuron growth, and the PI3K-Akt signaling pathway, which is related to cell proliferation and growth [153].

3.6.4. Epigenetic Findings

French researchers demonstrated that biomarkers related to lithium's beneficial effects could also be identified using epigenetic studies. A genome-wide methylomic approach (SeqCapEpi) revealed significant differences in methylation between LR and LNR [154]. The combination of three clinical factors – polarity of the first episode, psychotic symptoms, and family history of BD – enabled the identification of 70% of individuals based on their response to lithium [155]. When combined with epigenetic markers, this probability increased to 86% [156]. The confirmation of specific methylation patterns determining lithium response in BD came also from a recent study obtaining 130 differentially methylated positions and 16 differentially methylated regions in LR vs LNR [157].

4. Conclusions

This review, although not complete, shows that the possible mechanisms of lithium action are multifold. In the paper, the evolution of the views on these mechanisms starting in the mid-19th century was shown, trying to distinguish either old or new findings. However, it turned out that many apparent "old" mechanisms had their revival in research performed in the 21th century. Additionally, many eventually converged toward lithium inhibition of GSK-3β and PI, the mechanisms postulated in the 1980s/1990s. In 2013, Brown and Tracy assumed these mechanisms as the most important for lithium action on the cellular level [158], and in 2016, Malhi and Outhred, simply stated that the research in the 21st century cemented GSK-3β inhibition as a key mechanism underpinning the effects of lithium [159].

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Some lithium mechanisms showed in our review are related to the pathogenesis of BD. In many of them, such a relationship is tentative at most. On the other hand, some findings connected with the described mechanisms, can be used as the markers of lithium response. The development of molecular genetics can make it possible to include genetic markers for this purpose. Such accommodation would make a valuable addition to establishing the best candidates for long-term lithium therapy. This the most effective method of BD prophylaxis, has become recently greatly underutilized.

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References

1. Cade, J.F. Lithium Salts in the Treatment of Psychotic Excitement. *Med J Aust* **1949**, *2*, 349–352, doi:10.1080/j.1440-1614.1999.06241.x.
2. Hartigan, G.P. The Use of Lithium Salts in Affective Disorders. *The British Journal of Psychiatry* **1963**, *109*, 810–814, doi:10.1192/BJP.109.463.810.
3. Yatham, L.N.; Kennedy, S.H.; Parikh, S.V.; Schaffer, A.; Bond, D.J.; Frey, B.N.; Sharma, V.; Goldstein, B.I.; Rej, S.; Beaulieu, S.; et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 Guidelines for the Management of Patients with Bipolar Disorder. *Bipolar Disord* **2018**, *20*, 97–170, doi:10.1111/BDI.12609.
4. Bauer, M.; Adli, M.; Ricken, R.; Severus, E.; Pilhatsch, M. Role of Lithium Augmentation in the Management of Major Depressive Disorder. *CNS Drugs* **2014**, *28*, 331–342, doi:10.1007/s40263-014-0152-8.
5. Tondo, L.; Baldessarini, R.J. Prevention of Suicidal Behavior with Lithium Treatment in Patients with Recurrent Mood Disorders. *Int J Bipolar Disord* **2024**, *12*, doi:10.1186/S40345-024-00326-X.
6. Rybakowski, J.K. Antiviral, Immunomodulatory, and Neuroprotective Effect of Lithium. *J Integr Neurosci* **2022**, *21*, 68, doi:10.31083/J.JIN2102068/1757-448X-21-2-068.PDF.
7. Mandal, A.K.; Mount, D.B. The Molecular Physiology of Uric Acid Homeostasis. *Annu Rev Physiol* **2015**, *77*, 323–345, doi:10.1146/ANNUREV-PHYSIOL-021113-170343.
8. Garrod, A. *The Nature and Treatment of Gout, and Rheumatic Gout*; 1876;
9. Lange, C.G. *Om Periodiske Depressionstilstande Og Deres Patogenese....*; J. Lund: Copenhagen, 1886;
10. Anumonye, A.; Reading, H.W.; Knight, F.; Ashcroft, G.W. Uric-Acid Metabolism in Manic-Depressive Illness and during Lithium Therapy. *Lancet* **1968**, *1 7555*, 1290–1293, doi:10.1016/S0140-6736(68)92300-3.
11. Chung, K.H.; Huang, C.C.; Lin, H.C. Increased Risk of Gout among Patients with Bipolar Disorder: A Nationwide Population-Based Study. *Psychiatry Res* **2010**, *180*, 147–150, doi:10.1016/J.PSYCHRES.2009.07.012.
12. Chatterjee, S.S.; Ghosal, S.; Mitra, S.; Mallik, N.; Ghosal, M.K. Serum Uric Acid Levels in First Episode Mania, Effect on Clinical Presentation and Treatment Response: Data from a Case Control Study. *Asian J Psychiatr* **2018**, *35*, 15–17, doi:10.1016/J.AJP.2018.04.030.
13. Salvadore, G.; Viale, C.I.; Luckenbaugh, D.A.; Zanatto, V.C.; Portela, L.V.; Souza, D.O.; Zarate, C.A.; Machado-Vieira, R. Increased Uric Acid Levels in Drug-Naïve Subjects with Bipolar Disorder during a First Manic Episode. *Prog Neuropsychopharmacol Biol Psychiatry* **2010**, *34*, 819–821, doi:10.1016/J.PNPBP.2010.02.027.

14. Bartoli, F.; Crocamo, C.; Mazza, M.G.; Clerici, M.; Carrà, G. Uric Acid Levels in Subjects with Bipolar Disorder: A Comparative Meta-Analysis. *J Psychiatr Res* **2016**, *81*, 133–139, doi:10.1016/J.JPSYCHIRES.2016.07.007.
15. Muti, M.; Del Grande, C.; Musetti, L.; Marazziti, D.; Turri, M.; Cirronis, M.; Pergentini, I.; Corsi, M.; Dell'Osso, L.; Corsini, G.U. Serum Uric Acid Levels and Different Phases of Illness in Bipolar I Patients Treated with Lithium. *Psychiatry Res* **2015**, *225*, 604–608, doi:10.1016/J.PSYCHRES.2014.11.038.
16. Burnstock, G. The Past, Present and Future of Purine Nucleotides as Signalling Molecules. *Neuropharmacology* **1997**, *36*, 1127–1139, doi:10.1016/S0028-3908(97)00125-1.
17. Gubert, C.; Jacintho Moritz, C.E.; Vasconcelos-Moreno, M.P.; Quadros dos Santos, B.T.M.; Sartori, J.; Fijtman, A.; Kauer-Sant'Anna, M.; Kapczinski, F.; Battastini, A.M.O.; Magalhães, P.V. da S. Peripheral Adenosine Levels in Euthymic Patients with Bipolar Disorder. *Psychiatry Res* **2016**, *246*, 421–426, doi:10.1016/J.PSYCHRES.2016.10.007.
18. Wilot, L.C.; Bernardi, A.; Frozza, R.L.; Marques, A.L.; Cimarosti, H.; Salbego, C.; Rocha, E.; Battastini, A.M.O. Lithium and Valproate Protect Hippocampal Slices against ATP-Induced Cell Death. *Neurochem Res* **2007**, *32*, 1539–1546, doi:10.1007/S11064-007-9348-3.
19. Gubert, C.; Rodrigo Fries, G.; Wollenhaupt de Aguiar, B.; Ribeiro Rosa, A.; Busnello, V.; Ribeiro, L.; Bueno Morrone, F.; Maria Oliveira Battastini, A.; Kapczinski, F. The P2X7 Purinergic Receptor as a Molecular Target in Bipolar Disorder. **2013**, *8*, 1–7.
20. Gubert, C.; Andrejew, R.; Jacintho Moritz, C.E.; Dietrich, F.; Vasconcelos-Moreno, M.P.; dos Santos, B.T.M.Q.; Fijtman, A.; Kauer-Sant'Anna, M.; Kapczinski, F.; da Silva Magalhães, P.V.; et al. Bipolar Disorder and 1513A>C P2RX7 Polymorphism Frequency. *Neurosci Lett* **2019**, *694*, 143–147, doi:10.1016/J.NEULET.2018.11.055.
21. Gubert, C.; Andrejew, R.; Figueiro, F.; Bergamin, L.; Kapczinski, F.; Magalhães, P.V. da S.; Battastini, A.M.O. Lithium-Induced Neuroprotective Activity in Neuronal and Microglial Cells: A Purinergic Perspective. *Psychiatry Res* **2021**, *295*, doi:10.1016/J.PSYCHRES.2020.113562.
22. Serry, M. Lithium Retention and Response. *Lancet* **1969**, *1*, 1267–1268, doi:10.1016/S0140-6736(69)92148-5.
23. Serry, M. The Lithium Excretion Test: I. Clinical Application and Interpretation. *Aust N Z J Psychiatry* **1969**, *3*, 390–394, doi:10.1080/00048676909159293.
24. Haas, M.; Schooler, J.; Tosteson, D.C. Coupling of Lithium to Sodium Transport in Human Red Cells. *Nature* **1975**, *258*, 425–427, doi:10.1038/258425A0.
25. Rybakowski, J.; Frazer, A.; Mendels, J.; Alan Ramsey, T. Prediction of the Lithium Ratio in Man by Means of an in Vitro Test. *Clin Pharmacol Ther* **1977**, *22*, 465–469, doi:10.1002/CPT1977224465.
26. Rybakowski, J.; Frazer, A.; Mendels, J.; Ramsey, T.A. Erythrocyte Accumulation of the Lithium Ion in Control Subjects and Patients with Primary Affective Disorder. *Commun Psychopharmacol* **1978**, *2*, 99–104.
27. Dorus, E.; Pandey, G.N.; Shaughnessy, R.; Davis, J.M. Lithium Transport across the RBC Membrane. A Study of Genetic Factors. *Arch Gen Psychiatry* **1980**, *37*, 80–81, doi:10.1001/ARCHPSYC.1980.01780140082009.
28. Pandey, G.N.; Dorus, E.; Casper, R.C.; Janicek, P.; Davis, J.M. Lithium Transport in Red Cells of Patients with Affective Disorders. *Prog Neuropsychopharmacol Biol Psychiatry* **1984**, *8*, 547–555, doi:10.1016/0278-5846(84)90014-9.
29. Hokin-Neaverson, M.; Jefferson, J.W. Deficient Erythrocyte NaK-ATPase Activity in Different Affective States in Bipolar Affective Disorder and Normalization by Lithium Therapy. *Neuropsychobiology* **1989**, *22*, 18–25, doi:10.1159/000118587.
30. Rybakowski, J.; Potok, E.; Strzyzewski, W.; Chłopocka-Woźniak, M. The Effects of Lithium Treatment on Cation Transport Processes in Erythrocytes of Patients with Affective Illnesses. *Pol J Pharmacol Pharm* **1983**, *35*, 209–215.
31. Rybakowski, J.; Potok, E.; Strzyzewski, W. Decreased Activity of Ouabain-Dependent Sodium and Potassium Fluxes in Erythrocytes during Depression and Mania. *Act Nerv Super (Praha)* **1983**, *25*, 72–74.
32. Naylor, G.J.; Smith, A.H.W.; Dick, E.G.; Dick, D.A.T.; McHarg, A.M.; Chambers, C.A. Erythrocyte Membrane Cation Carrier in Manic-Depressive Psychosis. *Psychol Med* **1980**, *10*, 521–525, doi:10.1017/S0033291700047413.

 doi:10.20944/preprints202501.0302.v1

33. El-Mallakh, R.S.; Wyatt, R.J. The Na,K-ATPase Hypothesis for Bipolar Illness. *Biol Psychiatry* **1995**, *37*, 235–244, doi:10.1016/0006-3223(94)00201-D.
34. Mynett-Johnson, L.; Murphy, V.; McCormack, J.; Shields, D.C.; Claffey, E.; Manley, P.; McKeon, P. Evidence for an Allelic Association between Bipolar Disorder and a Na+, K+ Adenosine Triphosphatase Alpha Subunit Gene (ATP1A3). *Biol Psychiatry* **1998**, *44*, 47–51, doi:10.1016/S0006-3223(97)00343-0.
35. Goldstein, I.; Lerer, E.; Laiba, E.; Mallet, J.; Mujaheed, M.; Laurent, C.; Rosen, H.; Ebstein, R.P.; Lichtstein, D. Association between Sodium- and Potassium-Activated Adenosine Triphosphatase Alpha Isoforms and Bipolar Disorders. *Biol Psychiatry* **2009**, *65*, 985–991, doi:10.1016/J.BIOPSYCH.2008.10.033.
36. Newton, A.C.; Bootman, M.D.; Scott, J. Second Messengers. *Cold Spring Harb Perspect Biol* **2016**, *8*, doi:10.1101/CSHPERSPECT.A005926.
37. Sutherland, E.W. Studies on the Mechanism of Hormone Action. *Science (1979)* **1972**, *177*, 401–408, doi:10.1126/SCIENCE.177.4047.401/ASSET/8A3D20D6-1B19-4F87-8151-4748943F3D55/ASSETS/SCIENCE.177.4047.401.FP.PNG.
38. Hepler, J.R.; Gilman, A.G. G Proteins. *Trends Biochem Sci* **1992**, *17*, 383–387, doi:10.1016/0968-0004(92)90005-T.
39. Newman, M.E.; Belmaker, R.H. Effects of Lithium in Vitro and Ex Vivo on Components of the Adenylate Cyclase System in Membranes from the Cerebral Cortex of the Rat. *Neuropharmacology* **1987**, *26*, 211–217, doi:10.1016/0028-3908(87)90211-5.
40. Colin, S.F.; Chang, H.C.; Mollner, S.; Pfeuffer, T.; Reed, R.R.; Duman, R.S.; Nestler, E.J. Chronic Lithium Regulates the Expression of Adenylate Cyclase and Gi-Protein Alpha Subunit in Rat Cerebral Cortex. *Proc Natl Acad Sci U S A* **1991**, *88 23*, 10634–10637, doi:10.1073/PNAS.88.23.10634.
41. Harvey, B.; Carstens, M.; Taljaard, J. Lithium Modulation of Cortical Cyclic Nucleotides: Evidence for the Yin-Yang Hypothesis. *Eur J Pharmacol* **1990**, *175 2*, 129–136, doi:10.1016/0014-2999(90)90223-S.
42. Mann, L.; Heldman, E.; Bersudsky, Y.; Vatner, S.F.; Ishikawa, Y.; Almog, O.; Belmaker, R.H.; Agam, G. Inhibition of Specific Adenylyl Cyclase Isoforms by Lithium and Carbamazepine, but Not Valproate, May Be Related to Their Antidepressant Effect. *Bipolar Disord* **2009**, *11*, 885–896, doi:10.1111/J.1399-5618.2009.00762.X.
43. Mühleisen, T.W.; Leber, M.; Schulze, T.G.; Strohmaier, J.; Degenhardt, F.; Treutlein, J.; Mattheisen, M.; Forstner, A.J.; Schumacher, J.; Breuer, R.; et al. Genome-Wide Association Study Reveals Two New Risk Loci for Bipolar Disorder. *Nat Commun* **2014**, *5*, doi:10.1038/NCOMMS4339.
44. Aghabozorg Afjeh, S.S.; Shams, J.; Hamednia, S.; Boshehri, B.; Olfat, A.; Omrani, M.D. Investigation of the Impact of an ADCY2 Polymorphism as a Predictive Biomarker in Bipolar Disorder, Suicide Tendency and Response to Lithium Carbonate Therapy: The First Report from Iran. *Pharmacogenomics* **2020**, *21*, 1011–1020, doi:10.2217/PGS-2020-0058.
45. Hallcher, L.M.; Sherman, W.R. The Effects of Lithium Ion and Other Agents on the Activity of Myo-Inositol-1-Phosphatase from Bovine Brain. *J Biol Chem* **1980**, *255*, 10896–10901.
46. Berridge, M.J.; Downes, C.P.; Hanley, M.R. Neural and Developmental Actions of Lithium: A Unifying Hypothesis. *Cell* **1989**, *59*, 411–419, doi:10.1016/0092-8674(89)90026-3.
47. Ding, D.; Greenberg, M.L. Lithium and Valproate Decrease the Membrane Phosphatidylinositol/Phosphatidylcholine Ratio. *Mol Microbiol* **2003**, *47*, 373–381, doi:10.1046/J.1365-2958.2003.03284.X.
48. Soares, J.C.; Mallinger, A.G.; Dippold, C.S.; Frank, E.; Kupfer, D.J. Platelet Membrane Phospholipids in Euthymic Bipolar Disorder Patients: Are They Affected by Lithium Treatment? *Biol Psychiatry* **1999**, *45*, 453–457, doi:10.1016/S0006-3223(98)00048-1.
49. Soares, J.C.; Chen, G.; Dippold, C.S.; Wells, K.F.; Frank, E.; Kupfer, D.J.; Manji, H.K.; Mallinger, A.G. Concurrent Measures of Protein Kinase C and Phosphoinositides in Lithium-Treated Bipolar Patients and Healthy Individuals: A Preliminary Study. *Psychiatry Res* **2000**, *95*, 109–118, doi:10.1016/S0165-1781(00)00175-X.
50. Agam, G.; Bersudsky, Y.; Berry, G.T.; Moechars, D.; Lavi-Avnon, Y.; Belmaker, R.H. Knockout Mice in Understanding the Mechanism of Action of Lithium. *Biochem Soc Trans* **2009**, *37*, 1121–1125, doi:10.1042/BST0371121.

51. Baum, A.E.; Akula, N.; Cabanero, M.; Cardona, I.; Corona, W.; Klemens, B.; Schulze, T.G.; Cichon, S.; Rietschel, M.; Nöthen, M.M.; et al. A Genome-Wide Association Study Implicates Diacylglycerol Kinase Eta (DGKH) and Several Other Genes in the Etiology of Bipolar Disorder. *Mol Psychiatry* **2008**, *13*, 197–207, doi:10.1038/SJ.MP.4002012.
52. Bloch, P.J.; Weller, A.E.; Doyle, G.A.; Ferraro, T.N.; Berrettini, W.H.; Hodge, R.; Lohoff, F.W. Association Analysis between Polymorphisms in the Myo-Inositol Monophosphatase 2 (IMPA2) Gene and Bipolar Disorder. *Prog Neuropsychopharmacol Biol Psychiatry* **2010**, *34*, 1515–1519, doi:10.1016/J.PNPBP.2010.08.015.
53. Beurel, E.; Grieco, S.F.; Jope, R.S. Glycogen Synthase Kinase-3 (GSK3): Regulation, Actions, and Diseases. *Pharmacol Ther* 2015, *148*, 114–131.
54. Klein, P.S.; Melton, D.A. A Molecular Mechanism for the Effect of Lithium on Development. *Proc Natl Acad Sci U S A* **1996**, *93*, 8455–8459, doi:10.1073/PNAS.93.16.8455.
55. Stambolic, V.; Ruel, L.; Woodgett, J.R. Lithium Inhibits Glycogen Synthase Kinase-3 Activity and Mimics Wingless Signalling in Intact Cells. *Current Biology* **1996**, *6*, 1664–1669, doi:10.1016/S0960-9822(02)70790-2.
56. Chatterjee, D.; Beaulieu, J.M. Inhibition of Glycogen Synthase Kinase 3 by Lithium, a Mechanism in Search of Specificity. *Front Mol Neurosci* **2022**, *15*, doi:10.3389/FNMOL.2022.1028963.
57. Tian, N.; Kanno, T.; Jin, Y.; Nishizaki, T. Lithium Potentiates GSK-3β Activity by Inhibiting Phosphoinositide 3-Kinase-Mediated Akt Phosphorylation. *Biochem Biophys Res Commun* **2014**, *450 1*, 746–749, doi:10.1016/J.BBRC.2014.06.041.
58. Mullins, N.; Forstner, A.J.; O'Connell, K.S.; Coombes, B.; Coleman, J.R.I.; Qiao, Z.; Als, T.D.; Bigdeli, T.B.; Børte, S.; Bryois, J.; et al. Genome-Wide Association Study of More than 40,000 Bipolar Disorder Cases Provides New Insights into the Underlying Biology. *Nat Genet* **2021**, *53*, 817–829, doi:10.1038/S41588-021-00857-4.
59. Rybakowski, J.K.; Abramowicz, M.; Szczepankiewicz, A.; Michalak, M.; Hauser, J.; Czekalski, S. The Association of Glycogen Synthase Kinase-3beta (GSK-3β) Gene Polymorphism with Kidney Function in Long-Term Lithium-Treated Bipolar Patients. *Int J Bipolar Disord* **2013**, *1*, 1–5, doi:10.1186/2194-7511-1-8.
60. Malhi, G.S.; Das, P.; Outhred, T.; Irwin, L.; Morris, G.; Hamilton, A.; Lynch, K.; Mannie, Z. Understanding Suicide: Focusing on Its Mechanisms through a Lithium Lens. *J Affect Disord* **2018**, *241*, 338–347, doi:10.1016/J.JAD.2018.08.036.
61. Barde, Y.A.; Edgar, D.; Thoenen, H. Purification of a New Neurotrophic Factor from Mammalian Brain. *EMBO J* **1982**, *1*, 549–553, doi:10.1002/J.1460-2075.1982.TB01207.X.
62. Hashimoto, K. Brain-Derived Neurotrophic Factor as a Biomarker for Mood Disorders: An Historical Overview and Future Directions. *Psychiatry Clin Neurosci* **2010**, *64*, 341–357, doi:10.1111/J.1440-1819.2010.02113.X.
63. Li, M.; Chang, H.; Xiao, X. BDNF Val66Met Polymorphism and Bipolar Disorder in European Populations: A Risk Association in Case-Control, Family-Based and GWAS Studies. *Neurosci Biobehav Rev* **2016**, *68*, 218–233, doi:10.1016/J.NEUBIOREV.2016.05.031.
64. Fukumoto, T.; Morinobu, S.; Okamoto, Y.; Kagaya, A.; Yamawaki, S. Chronic Lithium Treatment Increases the Expression of Brain-Derived Neurotrophic Factor in the Rat Brain. *Psychopharmacology (Berl)* **2001**, *158*, 100–106, doi:10.1007/S002130100871.
65. Kauer-Sant'Anna, M.; Kapczinski, F.; Andreazza, A.C.; Bond, D.J.; Lam, R.W.; Young, L.T.; Yatham, L.N. Brain-Derived Neurotrophic Factor and Inflammatory Markers in Patients with Early- vs. Late-Stage Bipolar Disorder. *International Journal of Neuropsychopharmacology* **2009**, *12*, 447–458, doi:10.1017/S1461145708009310.
66. Rybakowski, J.K.; Suwalska, A. Excellent Lithium Responders Have Normal Cognitive Functions and Plasma BDNF Levels. *Int J Neuropsychopharmacol* **2010**, *13*, 617–622, doi:10.1017/S1461145710000404.
67. Rybakowski, J.K.; Borkowska, A.; Skibinska, M.; Hauser, J. Illness-Specific Association of Val66met BDNF Polymorphism with Performance on Wisconsin Card Sorting Test in Bipolar Mood Disorder. *Mol Psychiatry* **2006**, *11*, 122–124, doi:10.1038/SJ.MP.4001765.
68. Rybakowski, J.K.; Suwalska, A.; Skibinska, M.; Dmitrzak-Weglarz, M.; Leszczynska-Rodziewicz, A.; Hauser, J. Response to Lithium Prophylaxis: Interaction between Serotonin Transporter and BDNF Genes.

American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics **2007**, *144*, 820–823, doi:10.1002/ajmg.b.30420.

69. Schildkraut, J.J. The Catecholamine Hypothesis of Affective Disorders: A Review of Supporting Evidence. *Am J Psychiatry* **1965**, *122*, 509–522, doi:10.1176/AJP.122.5.509.
70. Bunney, W.E. The Current Status of Research in the Catecholamine Theories of Affective Disorders. *Psychopharmacol Commun* **1975**, *1*, 599–609.
71. Coppen, A. Defects in Monoamine Metabolism and Their Possible Importance in the Pathogenesis of Depressive Syndromes. *Psychiatr Neurol Neurochir* **1969**, *72*, 173–180.
72. Ashok, A.H.; Marques, T.R.; Jauhar, S.; Nour, M.M.; Goodwin, G.M.; Young, A.H.; Howes, O.D. The Dopamine Hypothesis of Bipolar Affective Disorder: The State of the Art and Implications for Treatment. *Mol Psychiatry* **2017**, *22*, 666–679, doi:10.1038/MP.2017.16.
73. Gallager, D.W.; Pert, A.; Bunney, W.E. Haloperidol-Induced Presynaptic Dopamine Supersensitivity Is Blocked by Chronic Lithium. *Nature* **1978**, *273*, 309–312, doi:10.1038/273309A0.
74. Can, A.; Frost, D.O.; Cachope, R.; Cheer, J.F.; Gould, T.D. Chronic Lithium Treatment Rectifies Maladaptive Dopamine Release in the Nucleus Accumbens. *J Neurochem* **2016**, *139*, 576–585, doi:10.1111/JNC.13769.
75. Beaulieu, J.M. Converging Evidence for Regulation of Dopamine Neurotransmission by Lithium: An Editorial Highlight for "Chronic Lithium Treatment Rectifies Maladaptive Dopamine Release in the Nucleus Accumbens." *J Neurochem* **2016**, *139*, 520–522, doi:10.1111/JNC.13846.
76. Mohamadian, M.; Fallah, H.; Ghofrani-Jahromi, Z.; Rahimi-Danesh, M.; Shokouhi Qare Saadlou, M.S.; Vaseghi, S. Mood and Behavior Regulation: Interaction of Lithium and Dopaminergic System. *Naunyn Schmiedebergs Arch Pharmacol* **2023**, *396*, 1339–1359, doi:10.1007/S00210-023-02437-1.
77. Muller-Oerlinghausen, B. Lithium Long-Term Treatment--Does It Act via Serotonin? *Pharmacopsychiatry* **1985**, *18*, 214–217, doi:10.1055/S-2007-1017367.
78. Price, L.H.; Charney, D.S.; Delgado, P.L.; Heninger, G.R. Lithium and Serotonin Function: Implications for the Serotonin Hypothesis of Depression. *Psychopharmacology (Berl)* **1990**, *100*, 3–12, doi:10.1007/BF02245781.
79. Ananth, M.; Bartlett, E.A.; DeLorenzo, C.; Lin, X.; Kunkel, L.; Vadhan, N.P.; Perlman, G.; Godstrey, M.; Holzmacher, D.; Ogden, R.T.; et al. Prediction of Lithium Treatment Response in Bipolar Depression Using 5-HTT and 5-HT1A PET. *Eur J Nucl Med Mol Imaging* **2020**, *47*, 2417–2428, doi:10.1007/S00259-020-04681-6.
80. Li, X.; Friedman, A.B.; Zhu, W.; Wang, L.; Boswell, S.; May, R.S.; Davis, L.L.; Jope, R.S. Lithium Regulates Glycogen Synthase Kinase-3β in Human Peripheral Blood Mononuclear Cells: Implication in the Treatment of Bipolar Disorder. *Biol Psychiatry* **2007**, *61*, 216–222, doi:10.1016/j.biopsych.2006.02.027.
81. Wu, T.N.; Lee, C.S.; Wu, B.J.; Sun, H.J.; Chang, C.H.; Chen, C.Y.; Chen, C.K.; Wu, L.S.H.; Cheng, A.T.A. Immunophenotypes Associated with Bipolar Disorder and Lithium Treatment. *Sci Rep* **2019**, *9*, doi:10.1038/s41598-019-53745-7.
82. Ling, P.D.; Huls, H.M. Isolation and Immortalization of Lymphocytes. *Curr Protoc Mol Biol* **2005**, *Chapter 28*, doi:10.1002/0471142727.MB2802S70.
83. Fries, G.R.; Colpo, G.D.; Monroy-Jaramillo, N.; Zhao, J.; Zhao, Z.; Arnold, J.G.; Bowden, C.L.; Walss-Bass, C. Distinct Lithium-Induced Gene Expression Effects in Lymphoblastoid Cell Lines from Patients with Bipolar Disorder. *European Neuropsychopharmacology* **2017**, *27*, 1110–1119, doi:10.1016/J.EURONEURO.2017.09.003.
84. Squassina, A.; Costa, M.; Congiu, D.; Manchia, M.; Angius, A.; Deiana, V.; Ardau, R.; Chillotti, C.; Severino, G.; Calza, S.; et al. Insulin-like Growth Factor 1 (IGF-1) Expression Is up-Regulated in Lymphoblastoid Cell Lines of Lithium Responsive Bipolar Disorder Patients. *Pharmacol Res* **2013**, *73*, 1–7, doi:10.1016/J.PHRS.2013.04.004.
85. Paul, P.; Iyer, S.; Nadella, R.K.; Nayak, R.; Chellappa, A.S.; Ambardar, S.; Sud, R.; Sukumaran, S.K.; Purushottam, M.; Jain, S.; et al. Lithium Response in Bipolar Disorder Correlates with Improved Cell Viability of Patient Derived Cell Lines. *Sci Rep* **2020**, *10*, doi:10.1038/S41598-020-64202-1.
86. Milanesi, E.; Voinsky, I.; Hadar, A.; Srouji, A.; Maj, C.; Shekhtman, T.; Gershovits, M.; Gilad, S.; Chillotti, C.; Squassina, A.; et al. RNA Sequencing of Bipolar Disorder Lymphoblastoid Cell Lines Implicates the Neurotrophic Factor HRP-3 in Lithium's Clinical Efficacy. *World J Biol Psychiatry* **2019**, *20*, 449–461, doi:10.1080/15622975.2017.1372629.

87. Mizrahi, L.; Choudhary, A.; Ofer, P.; Goldberg, G.; Milanesi, E.; Kelsoe, J.R.; Gurwitz, D.; Alda, M.; Gage, F.H.; Stern, S. Immunoglobulin Genes Expressed in Lymphoblastoid Cell Lines Discern and Predict Lithium Response in Bipolar Disorder Patients. *Mol Psychiatry* **2023**, *28*, 4280–4293, doi:10.1038/S41380-023-02183-Z.
88. Chen, H.; Wang, N.; Burmeister, M.; McInnis, M.G. MicroRNA Expression Changes in Lymphoblastoid Cell Lines in Response to Lithium Treatment. *Int J Neuropsychopharmacol* **2009**, *12*, 975–981, doi:10.1017/S1461145709000029.
89. Cattane, N.; Courtin, C.; Mombelli, E.; Maj, C.; Mora, C.; Etain, B.; Bellivier, F.; Marie-Claire, C.; Cattaneo, A. Transcriptomics and MiRNomics Data Integration in Lymphoblastoid Cells Highlights the Key Role of Immune-Related Functions in Lithium Treatment Response in Bipolar Disorder. *BMC Psychiatry* **2022**, *22*, doi:10.1186/S12888-022-04286-3.
90. Kuijk, E.W.; Chuva de Sousa Lopes, S.M.; Geijsen, N.; Macklon, N.; Roelen, B.A.J. The Different Shades of Mammalian Pluripotent Stem Cells. *Hum Reprod Update* **2011**, *17 2*, 254–271, doi:10.1093/HUMUPD/DMQ035.
91. Mertens, J.; Wang, Q.W.; Kim, Y.; Yu, D.X.; Pham, S.; Yang, B.; Zheng, Y.; Diffenderfer, K.E.; Zhang, J.; Soltani, S.; et al. Differential Responses to Lithium in Hyperexcitable Neurons from Patients with Bipolar Disorder. *Nature 2015 527:7576* **2015**, *527*, 95–99, doi:10.1038/nature15526.
92. Stern, S.; Santos, R.; Marchetto, M.C.; Mendes, A.P.D.; Rouleau, G.A.; Biesmans, S.; Wang, Q.W.; Yao, J.; Charnay, P.; Bang, A.G.; et al. Neurons Derived from Patients with Bipolar Disorder Divide into Intrinsically Different Sub-Populations of Neurons, Predicting the Patients' Responsiveness to Lithium. *Mol Psychiatry* **2018**, *23*, 1453–1465, doi:10.1038/MP.2016.260.
93. Osete, J.R.; Akkouh, I.A.; de Assis, D.R.; Szabo, A.; Frei, E.; Hughes, T.; Smeland, O.B.; Steen, N.E.; Andreassen, O.A.; Djurovic, S. Lithium Increases Mitochondrial Respiration in IPSC-Derived Neural Precursor Cells from Lithium Responders. *Mol Psychiatry* **2021**, *26*, 6789–6805, doi:10.1038/s41380-021-01164-4.
94. Khayachi, A.; Abuzgaya, M.; Liu, Y.; Jiao, C.; Dejgaard, K.; Schorova, L.; Kamesh, A.; He, Q.; Cousineau, Y.; Pietrantonio, A.; et al. Molecular Signatures of Hyperexcitability and Lithium Responsiveness in Bipolar Disorder Patient Neurons Provide Alternative Therapeutic Strategies. *bioRxiv* **2023**, 2023.07.21.550088, doi:10.1101/2023.07.21.550088.
95. Mishra, H.K.; Mandyam, A.D.; Trenet, W.; Wei, H.; Nievergelt, C.M.; Maihofer, A.X.; Shilling, P.D.; Alda, M.; Gershon, E.; McInnis, M.G.; et al. Neural Progenitor Cells Derived from Lithium Responsive and Non-Responsive Bipolar Disorder Patients Exhibit Distinct Sensitivity to Cell Death Following Methamphetamine. *Neuropharmacology* **2023**, *226*, doi:10.1016/J.NEUROPHARM.2022.109410.
96. Santos, R.; Linker, S.B.; Stern, S.; Mendes, A.P.D.; Shokhirev, M.N.; Erikson, G.; Randolph-Moore, L.; Racha, V.; Kim, Y.; Kelsoe, J.R.; et al. Deficient LEF1 Expression Is Associated with Lithium Resistance and Hyperexcitability in Neurons Derived from Bipolar Disorder Patients. *Mol Psychiatry* **2021**, *26*, 2440–2456, doi:10.1038/S41380-020-00981-3.
97. Saha, S.; Krishnan, H.; Raghu, P. IMPA1 Dependent Regulation of Phosphatidylinositol 4,5-Bisphosphate and Calcium Signalling by Lithium. *Life Sci Alliance* **2023**, *7*, doi:10.26508/LSA.202302425.
98. Grandin, L.D.; Alloy, L.B.; Abramson, L.Y. The Social Zeitgeber Theory, Circadian Rhythms, and Mood Disorders: Review and Evaluation. *Clin Psychol Rev* **2006**, *26*, 679–694, doi:10.1016/J.CPR.2006.07.001.
99. Jagannath, A.; Taylor, L.; Wakaf, Z.; Vasudevan, S.R.; Foster, R.G. The Genetics of Circadian Rhythms, Sleep and Health. *Hum Mol Genet* **2017**, *26*, 128–138, doi:10.1093/HMG/DDX240.
100. Roybal, K.; Theobold, D.; Graham, A.; DiNieri, J.A.; Russo, S.J.; Krishnan, V.; Chakravarty, S.; Peevey, J.; Oehrlein, N.; Birnbaum, S.; et al. Mania-like Behavior Induced by Disruption of CLOCK. *Proc Natl Acad Sci U S A* **2007**, *104*, 6406–6411, doi:10.1073/PNAS.0609625104.
101. Freund, N.; Haussleiter, I. Bipolar Chronobiology in Men and Mice: A Narrative Review. *Brain Sci* **2023**, *13*, doi:10.3390/BRAINSCI13050738.
102. Moreira, J.; Geoffroy, P.A. Lithium and Bipolar Disorder: Impacts from Molecular to Behavioural Circadian Rhythms. *Chronobiol Int* **2016**, *33*, 351–373, doi:10.3109/07420528.2016.1151026.

 doi:10.20944/preprints202501.0302.v1

103. McCarthy, M.J.; Wei, H.; Nievergelt, C.M.; Stautland, A.; Maihofer, A.X.; Welsh, D.K.; Shilling, P.; Alda, M.; Alliey-Rodriguez, N.; Anand, A.; et al. Chronotype and Cellular Circadian Rhythms Predict the Clinical Response to Lithium Maintenance Treatment in Patients with Bipolar Disorder. *Neuropsychopharmacology* **2019**, *44*, 620–628, doi:10.1038/S41386-018-0273-8.
104. Federoff, M.; McCarthy, M.J.; Anand, A.; Berrettini, W.H.; Bertram, H.; Bhattacharjee, A.; Calkin, C.V.; Conroy, C.; Coryell, W.H.; D'Arcangelo, N.; et al. Correction of Depression-Associated Circadian Rhythm Abnormalities Is Associated with Lithium Response in Bipolar Disorder. *Bipolar Disord* **2022**, *24*, 521–529, doi:10.1111/BDI.13162.
105. Dopierała, E.; Chrobak, A.; Tereszko, A.; Rybakowski, J. Lithium Influence on Circadian Rhythm Assessed by the Composite Scale of Morningness in Remitted Bipolar Patients. *Pharmakother Psychiatr Neurol* **2017**, *33*, 9–20.
106. Mishra, H.K.; Wei, H.; Rohr, K.E.; Ko, I.; Nievergelt, C.M.; Maihofer, A.X.; Shilling, P.D.; Alda, M.; Berrettini, W.H.; Brennand, K.J.; et al. Contributions of Circadian Clock Genes to Cell Survival in Fibroblast Models of Lithium-Responsive Bipolar Disorder. *Eur Neuropsychopharmacol* **2023**, *74*, 1–14, doi:10.1016/J.EURONEURO.2023.04.009.
107. Rybakowski, J.K.; Dmitrzak-Weglarz, M.; Kliwicki, S.; Hauser, J. Polymorphism of Circadian Clock Genes and Prophylactic Lithium Response. *Bipolar Disord* **2014**, *16*, 151–158, doi:10.1111/BDI.12136.
108. Yin, L.; Wang, J.; Klein, P.S.; Lazar, M.A. Nuclear Receptor Rev-Erbα Is a Critical Lithium-Sensitive Component of the Circadian Clock. *Science (1979)* **2006**, *311*, 1002–1005, doi:10.1126/SCIENCE.1121613/SUPPL_FILE/YIN.SOM.PDF.
109. Li, J.; Lu, W.Q.; Beesley, S.; Loudon, A.S.I.; Meng, Q.J. Lithium Impacts on the Amplitude and Period of the Molecular Circadian Clockwork. *PLoS One* **2012**, *7*, doi:10.1371/JOURNAL.PONE.0033292.
110. Blackburn, E.H.; Greider, C.W.; Szostak, J.W. Telomeres and Telomerase: The Path from Maize, Tetrahymena and Yeast to Human Cancer and Aging. *Nature Medicine 2006 12:10* **2006**, *12*, 1133–1138, doi:10.1038/nm1006-1133.
111. Coutts, F.; Palmos, A.B.; Duarte, R.R.R.; de Jong, S.; Lewis, C.M.; Dima, D.; Powell, T.R. The Polygenic Nature of Telomere Length and the Anti-Ageing Properties of Lithium. *Neuropsychopharmacology 2018 44:4* **2018**, *44*, 757–765, doi:10.1038/s41386-018-0289-0.
112. Martinsson, L.; Wei, Y.; Xu, D.; Melas, P.A.; Mathe, A.A.; Schalling, M.; Lavebratt, C.; Backlund, L. Long-Term Lithium Treatment in Bipolar Disorder Is Associated with Longer Leukocyte Telomeres. *Transl Psychiatry* **2013**, *3*, doi:10.1038/TP.2013.37.
113. Pisanu, C.; Congiu, D.; Manchia, M.; Caria, P.; Cocco, C.; Dettori, T.; Frau, D.V.; Manca, E.; Meloni, A.; Nieddu, M.; et al. Differences in Telomere Length between Patients with Bipolar Disorder and Controls Are Influenced by Lithium Treatment. *Pharmacogenomics* **2020**, *21*, 533–540, doi:10.2217/PGS-2020-0028.
114. Ferensztajn-Rochowiak, E.; Kurczewska, E.; Rubiś, B.; Lulkiewicz, M.; Hołysz, H.; Rybakowski, F.; Rybakowski, J.K. Decreased Leucocyte Telomere Length in Male Patients with Chronic Bipolar Disorder: Lack of Effect of Long-Term Lithium Treatment. *Acta Neuropsychiatr* **2021**, *33*, 299–306, doi:10.1017/NEU.2021.20.
115. Squassina, A.; Pisanu, C.; Congiu, D.; Caria, P.; Frau, D.; Niola, P.; Melis, C.; Baggiani, G.; Lopez, J.P.; Cruceanu, C.; et al. Leukocyte Telomere Length Positively Correlates with Duration of Lithium Treatment in Bipolar Disorder Patients. *European Neuropsychopharmacology* **2016**, *26*, 1241–1247, doi:10.1016/J.EURONEURO.2016.03.020.
116. Lundberg, M.; Millischer, V.; Backlund, L.; Martinsson, L.; Stenvinkel, P.; Sellgren, C.M.; Lavebratt, C.; Schalling, M. Lithium and the Interplay Between Telomeres and Mitochondria in Bipolar Disorder. *Front Psychiatry* **2020**, *11*, doi:10.3389/FPSYT.2020.586083/PDF.
117. Mutz, J.; Wong, W.L.E.; Powell, T.R.; Young, A.H.; Dawe, G.S.; Lewis, C.M. The Duration of Lithium Use and Biological Ageing: Telomere Length, Frailty, Metabolomic Age and All-Cause Mortality. *Geroscience* **2024**, *46*, doi:10.1007/S11357-024-01142-Y.
118. Wei, Y. Bin; Backlund, L.; Wegener, G.; Mathé, A.A.; Lavebratt, C. Telomerase Dysregulation in the Hippocampus of a Rat Model of Depression: Normalization by Lithium. *International Journal of Neuropsychopharmacology* **2015**, *18*, 1–8, doi:10.1093/IJNP/PYV002.

 doi:10.20944/preprints202501.0302.v1

119. Ferensztajn-Rochowiak, E.; Rybakowski, J.K. The Effect of Lithium on Hematopoietic, Mesenchymal and Neural Stem Cells. *Pharmacol Rep* **2016**, *68*, 224–230, doi:10.1016/J.PHAREP.2015.09.005.
120. Radomski, J.L.; Fuyat, H.N.; Nelson, A.A.; Smith, P.K. THE TOXIC EFFECTS, EXCRETION AND DISTRIBUTION OF LITHIUM CHLORIDE. *Journal of Pharmacology and Experimental Therapeutics* **1950**, *100*.
121. Rosenblat, J.D.; McIntyre, R.S. Bipolar Disorder and Inflammation. *Psychiatric Clinics of North America* **2016**, *39*, 125–137, doi:10.1016/j.psc.2015.09.006.
122. Sakrajda, K.; Szczepankiewicz, A. Inflammation-Related Changes in Mood Disorders and the Immunomodulatory Role of Lithium. *Int J Mol Sci* **2021**, *22*, 1–15, doi:10.3390/ijms22041532.
123. Arumugam, S.; Qin, Y.; Liang, Z.; Han, S.N.; Boodapati, S.L.T.; Li, J.; Lu, Q.; Flavell, R.A.; Mehal, W.Z.; Ouyang, X. GSK3β Mediates the Spatiotemporal Dynamics of NLRP3 Inflammasome Activation. *Cell Death Differ* **2022**, *29*, 2060–2069, doi:10.1038/s41418-022-00997-y.
124. Sakrajda, K.; Bilska, K.; Czerski, P.M.; Narożna, B.; Dmitrzak-Węglarz, M.; Heilmann-Heimbach, S.; Brockschmidt, F.F.; Herms, S.; Nöthen, M.M.; Cichon, S.; et al. Abelson Helper Integration Site 1 Haplotypes and Peripheral Blood Expression Associates with Lithium Response and Immunomodulation in Bipolar Patients. *Psychopharmacology (Berl)* **2024**, *241*, 727–738, doi:10.1007/S00213-023-06505-5.
125. Sakrajda, K.; Langwiński, W.; Stachowiak, Z.; Ziarniak, K.; Narożna, B.; Szczepankiewicz, A. Immunomodulatory Effect of Lithium Treatment on in Vitro Model of Neuroinflammation. *Neuropharmacology* **2025**, *265*, 110238, doi:10.1016/j.neuropharm.2024.110238.
126. Lieb, J. Remission of Recurrent Herpes Infection during Therapy with Lithium. *N Engl J Med* **1979**, *301*, 942–942, doi:10.1056/NEJM197910253011711.
127. Skinner, G.R.B.; Hartley, C.; Buchan, A.; Harper, L.; Gallimore, P. The Effect of Lithium Chloride on the Replication of Herpes Simplex Virus. *Med Microbiol Immunol* **1980**, *168*, 139–148, doi:10.1007/BF02121762.
128. Rybakowski, J.K.; Amsterdam, J.D. Lithium Prophylaxis and Recurrent Labial Herpes Infections. *Lithium* **1991**, *2*, 43–47.
129. Itzhaki, R.F. Overwhelming Evidence for a Major Role for Herpes Simplex Virus Type 1 (HSV1) in Alzheimer's Disease (AD); Underwhelming Evidence Against. *Vaccines (Basel)* **2021**, *9*, doi:10.3390/VACCINES9060679.
130. Amsterdam, J.D.; García-España, F.; Rybakowski, J. Rates of Flu-like Infection in Patients with Affective Illness. *J Affect Disord* **1998**, *47*, 177–182, doi:10.1016/S0165-0327(97)00118-3.
131. Landén, M.; Larsson, H.; Lichtenstein, P.; Westin, J.; Song, J. Respiratory Infections during Lithium and Valproate Medication: A within-Individual Prospective Study of 50,000 Patients with Bipolar Disorder. *Int J Bipolar Disord* **2021**, *9*, doi:10.1186/S40345-020-00208-Y.
132. Nowak, J.K.; Walkowiak, J.; Wei, F.; Wang, W.; Beaulieu, J.-M.; Chuang, D.-M. Lithium and Coronaviral Infections. A Scoping Review. *F1000Research 2020 9:93* **2020**, *9*, 93, doi:10.12688/f1000research.22299.2.
133. Murru, A.; Manchia, M.; Hajek, T.; Nielsen, R.E.; Rybakowski, J.K.; Sani, G.; Schulze, T.G.; Tondo, L.; Bauer, M. Lithium's Antiviral Effects: A Potential Drug for CoViD-19 Disease? *Int J Bipolar Disord* **2020**, *8*, 1–9, doi:10.1186/S40345-020-00191-4/METRICS.
134. Spuch, C.; López-García, M.; Rivera-Baltanás, T.; Cabrera-Alvargonzález, J.J.; Gadh, S.; Rodrigues-Amorim, D.; Álvarez-Estévez, T.; Mora, A.; Iglesias-Martínez-Almeida, M.; Freiría-Martínez, L.; et al. Efficacy and Safety of Lithium Treatment in SARS-CoV-2 Infected Patients. *Front Pharmacol* **2022**, *13*, doi:10.3389/FPHAR.2022.850583.
135. De Picker, L.J.; Leboyer, M.; Geddes, J.R.; Morrens, M.; Harrison, P.J.; Taquet, M. Association between Serum Lithium Level and Incidence of COVID-19 Infection. *Br J Psychiatry* **2022**, *221*, 425–427, doi:10.1192/BJP.2022.42.
136. Grof, P.; Duffy, A.; Cavazzoni, P.; Grof, E.; Garnham, J.; MacDougall, M.; O'Donovan, C.; Alda, M. Is Response to Prophylactic Lithium a Familial Trait? *J Clin Psychiatry* **2002**, *63*, 942–947, doi:10.4088/JCP.V63N1013.
137. Rybakowski, J.K. Genetic Influences on Response to Mood Stabilizers in Bipolar Disorder: Current Status of Knowledge. *CNS Drugs* **2013**, *27*, 165–173, doi:10.1007/S40263-013-0040-7.

 doi:10.20944/preprints202501.0302.v1

138. Szczepankiewicz, A.; Narozna, B.; Rybakowski, J.K.; Kliwicki, S.; Czerski, P.; Dmitrzak-Węglarz, M.; Skibińska, M.; Twarowska-Hauser, J.; Pawlak, J. Genes Involved in Stress Response Influence Lithium Efficacy in Bipolar Patients. *Bipolar Disord* **2018**, *20*, 753–760, doi:10.1111/BDI.12639.
139. Senner, F.; Kohshour, M.O.; Abdalla, S.; Papiol, S.; Schulze, T.G. The Genetics of Response to and Side Effects of Lithium Treatment in Bipolar Disorder: Future Research Perspectives. *Front Pharmacol* **2021**, *12*, doi:10.3389/FPHAR.2021.638882.
140. Perlis, R.H.; Smoller, J.W.; Ferreira, M.A.R.; McQuillin, A.; Bass, N.; Lawrence, J.; Sachs, G.S.; Nimgaonkar, V.; Scolnick, E.M.; Gurling, H.; et al. A Genomewide Association Study of Response to Lithium for Prevention of Recurrence in Bipolar Disorder. *Am J Psychiatry* **2009**, *166*, 718–725, doi:10.1176/APPI.AJP.2009.08111633.
141. Chen, C.-H.; Lee, C.-S.; Lee, M.-T.M.; Ouyang, W.-C.; Chen, C.-C.; Chong, M.-Y.; Wu, J.-Y.; Tan, H.K.-L.; Lee, Y.-C.; Chuo, L.-J.; et al. Variant GADL1 and Response to Lithium Therapy in Bipolar I Disorder. *N Engl J Med* **2014**, *370*, 119–128, doi:10.1056/NEJMOA1212444.
142. Song, J.; Bergen, S.E.; Di Florio, A.; Karlsson, R.; Charney, A.; Ruderfer, D.M.; Stahl, E.A.; Chambert, K.D.; Moran, J.L.; Gordon-Smith, K.; et al. Genome-Wide Association Study Identifies SESTD1 as a Novel Risk Gene for Lithium-Responsive Bipolar Disorder. *Mol Psychiatry* **2016**, *21*, 1290–1297, doi:10.1038/MP.2015.165.
143. Wolter, J.M.; Le, B.D.; Matoba, N.; Lafferty, M.J.; Aygün, N.; Liang, D.; Courtney, K.; Song, J.; Piven, J.; Zylka, M.J.; et al. Cellular Genome-Wide Association Study Identifies Common Genetic Variation Influencing Lithium-Induced Neural Progenitor Proliferation. *Biol Psychiatry* **2023**, *93*, 8–17, doi:10.1016/J.BIOPSYCH.2022.08.014.
144. Schulze, T.G.; Alda, M.; Adli, M.; Akula, N.; Ardau, R.; Bui, E.T.; Chillotti, C.; Cichon, S.; Czerski, P.; Del Zompo, M.; et al. The International Consortium on Lithium Genetics (ConLiGen): An Initiative by the NIMH and IGSLI to Study the Genetic Basis of Response to Lithium Treatment. *Neuropsychobiology* **2010**, *62*, 72–78, doi:10.1159/000314708.
145. Hou, L.; Heilbronner, U.; Degenhardt, F.; Adli, M.; Akiyama, K.; Akula, N.; Ardau, R.; Arias, B.; Backlund, L.; Banzato, C.E.M.; et al. Genetic Variants Associated with Response to Lithium Treatment in Bipolar Disorder: A Genome-Wide Association Study. *Lancet* **2016**, *387*, 1085–1093, doi:10.1016/S0140-6736(16)00143-4.
146. Amare, A.T.; Schubert, K.O.; Hou, L.; Clark, S.R.; Papiol, S.; Heilbronner, U.; Degenhardt, F.; Tekola-Ayele, F.; Hsu, Y.H.; Shekhtman, T.; et al. Association of Polygenic Score for Schizophrenia and HLA Antigen and Inflammation Genes With Response to Lithium in Bipolar Affective Disorder: A Genome-Wide Association Study. *JAMA Psychiatry* **2018**, *75*, 65–74, doi:10.1001/JAMAPSYCHIATRY.2017.3433.
147. Dembińska-Krajewska, D.; Kliwicki, S.; Chłopocka-Woźniak, M.; Rybakowski, J. The Effectiveness of Prophylactic Use of Lithium in Bipolar Disorder and Schizotypal Traits (in Polish). *Pharmakother Psychiatr Neurol.* **2012**, *28*, 153–158.
148. Amare, A.T.; Schubert, K.O.; Hou, L.; Clark, S.R.; Papiol, S.; Cearns, M.; Heilbronner, U.; Degenhardt, F.; Tekola-Ayele, F.; Hsu, Y.H.; et al. Association of Polygenic Score for Major Depression with Response to Lithium in Patients with Bipolar Disorder. *Mol Psychiatry* **2021**, *26*, 2457–2470, doi:10.1038/S41380-020-0689-5.
149. Coombes, B.J.; Millischer, V.; Batzler, A.; Larrabee, B.; Hou, L.; Papiol, S.; Heilbronner, U.; Adli, M.; Akiyama, K.; Akula, N.; et al. Association of Attention-Deficit/Hyperactivity Disorder and Depression Polygenic Scores with Lithium Response: A Consortium for Lithium Genetics Study. *Complex Psychiatry* **2021**, *7*, 80–89, doi:10.1159/000519707.
150. Herrera-Rivero, M.; Adli, M.; Akiyama, K.; Akula, N.; Amare, A.T.; Ardau, R.; Arias, B.; Aubry, J.M.; Backlund, L.; Bellivier, F.; et al. Exploring the Genetics of Lithium Response in Bipolar Disorders. *Int J Bipolar Disord* **2024**, *12*, doi:10.1186/S40345-024-00341-Y.
151. Le Clerc, S.; Lombardi, L.; Baune, B.T.; Amare, A.T.; Schubert, K.O.; Hou, L.; Clark, S.R.; Papiol, S.; Cearns, M.; Heilbronner, U.; et al. HLA-DRB1 and HLA-DQB1 Genetic Diversity Modulates Response to Lithium in Bipolar Affective Disorders. *Sci Rep* **2021**, *11*, 70, doi:10.1038/S41598-021-97140-7.

152. Amare, A.T.; Thalamuthu, A.; Schubert, K.O.; Fullerton, J.M.; Ahmed, M.; Hartmann, S.; Papiol, S.; Heilbronner, U.; Degenhardt, F.; Tekola-Ayele, F.; et al. Association of Polygenic Score and the Involvement of Cholinergic and Glutamatergic Pathways with Lithium Treatment Response in Patients with Bipolar Disorder. *Mol Psychiatry* **2023**, *28*, 5251–5261, doi:10.1038/S41380-023-02149-1.
153. Ou, A.H.; Rosenthal, S.B.; Adli, M.; Akiyama, K.; Akula, N.; Alda, M.; Amare, A.T.; Ardau, R.; Arias, B.; Aubry, J.M.; et al. Lithium Response in Bipolar Disorder Is Associated with Focal Adhesion and PI3K-Akt Networks: A Multi-Omics Replication Study. *Transl Psychiatry* **2024**, *14*, doi:10.1038/S41398-024-02811-4.
154. Marie-Claire, C.; Lejeune, F.X.; Mundwiller, E.; Ulveling, D.; Moszer, I.; Bellivier, F.; Etain, B. A DNA Methylation Signature Discriminates between Excellent and Non-Response to Lithium in Patients with Bipolar Disorder Type 1. *Sci Rep* **2020**, *10*, doi:10.1038/S41598-020-69073-0.
155. Marie-Claire, C.; Courtin, C.; Bellivier, F.; Scott, J.; Etain, B. Methylomic Biomarkers of Lithium Response in Bipolar Disorder: A Proof of Transferability Study. *Pharmaceuticals (Basel)* **2022**, *15*, doi:10.3390/PH15020133.
156. Marie-Claire, C.; Courtin, C.; Bellivier, F.; Gard, S.; Leboyer, M.; Scott, J.; Etain, B. Methylomic Biomarkers of Lithium Response in Bipolar Disorder: A Clinical Utility Study. *Int J Bipolar Disord* **2023**, *11*, doi:10.1186/S40345-023-00296-6.
157. Zafrilla-López, M.; Acosta-Díez, M.; Mitjans, M.; Giménez-Palomo, A.; Saiz, P.A.; Barrot-Feixat, C.; Jiménez, E.; Papiol, S.; Ruiz, V.; Gavín, P.; et al. Lithium Response in Bipolar Disorder: Epigenome-Wide DNA Methylation Signatures and Epigenetic Aging. *Eur Neuropsychopharmacol* **2024**, *85*, 23–31, doi:10.1016/J.EURONEURO.2024.03.010.
158. Brown, K.M.; Tracy, D.K. Lithium: The Pharmacodynamic Actions of the Amazing Ion. *Ther Adv Psychopharmacol* **2013**, *3*, 163–176, doi:10.1177/2045125312471963.
159. Malhi, G.S.; Outhred, T. Therapeutic Mechanisms of Lithium in Bipolar Disorder: Recent Advances and Current Understanding. *CNS Drugs 2016 30:10* **2016**, *30*, 931–949, doi:10.1007/S40263-016-0380-1.