

ASSOCIATE EDITOR: ROBERT DANTZER

New Advances in the Pharmacology and Toxicology of Lithium: A Neurobiologically Oriented Overview

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This work was supported by Grant PID2019-105136RB-100 funded by MCIN/AEI/10.13039/501100011033 and by “ERDF A way of making Europe” (to A.B.). M.B. is supported by a NHMRC Senior Principal Research Fellowship and Leadership 3 Investigator Grant (1156072 and 2017131). G.F.’s work is supported by a fellowship from “La Caixa” Foundation (ID 100010434 - fellowship code LCF/BQ/DR21/11880019).

E.V. has received grants and served as consultant, advisor, or CME speaker for the following entities: AB-Biotics, AbbVie, Angelini, Biogen, Biohaven, Boehringer-Ingelheim, Celon Pharma, Compass, Dainippon Sumitomo Pharma, Ethypharm, Ferrer, Gedeon Richter, GH Research, Glaxo-Smith Kline, Idorsia, Janssen, Lundbeck, MedinCell, Novartis, Orion Corporation, Organon, Otsuka, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, and Viatrix outside the submitted work. G.F. has received CME-related honoraria or consulting fees from Angelini, Janssen-Cilag, and Lundbeck, Abbot. A.B. has received grants and served as a consultant for miCure Therapeutics. The other authors do not have an actual or perceived conflict of interest with the contents of this article.

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dx.doi.org/10.1124/pharmrev.120.000007.

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Abstract—Over the last six decades, lithium has been considered the gold standard treatment for the long-term management of bipolar disorder due to its efficacy in preventing both manic and depressive episodes as well as suicidal behaviors. Nevertheless, despite numerous observed effects on various cellular pathways and biologic systems, the precise mechanism through which lithium stabilizes mood remains elusive. Furthermore, there is recent support for the therapeutic potential of lithium in other brain diseases. This review offers a comprehensive examination of contemporary understanding and predominant theories concerning the diverse mechanisms underlying lithium's effects. These findings are based on investigations utilizing cellular and animal models of neurodegenerative and psychiatric disorders. Recent studies have provided additional support for the significance of glycogen synthase kinase-3 (GSK3) inhibition as a crucial mechanism. Furthermore, research has shed more light on the interconnections between GSK3-mediated neuroprotective, antioxidant, and neuroplasticity processes. Moreover, recent advancements in animal and human models have provided valu-

able insights into how lithium-induced modifications at the homeostatic synaptic plasticity level may play a pivotal role in its clinical effectiveness. We focused on findings from translational studies suggesting that lithium may interface with microRNA expression. Finally, we are exploring the repurposing potential of lithium beyond bipolar disorder. These recent findings on the therapeutic mechanisms of lithium have provided important clues toward developing predictive models of response to lithium treatment and identifying new biologic targets.

Significance Statement—Lithium is the drug of choice for the treatment of bipolar disorder, but its mechanism of action in stabilizing mood remains elusive. This review presents the latest evidence on lithium's various mechanisms of action. Recent evidence has strengthened glycogen synthase kinase-3 (GSK3) inhibition, changes at the level of homeostatic synaptic plasticity, and regulation of microRNA expression as key mechanisms, providing an intriguing perspective that may help bridge the mechanistic gap between molecular functions and its clinical efficacy as a mood stabilizer.

ABBREVIATIONS: AD, Alzheimer disease; Akt, serine/threonine kinase; ALS, amyotrophic lateral sclerosis; AMPAR, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; A β , β -amyloid; Bcl-2, B-cell lymphoma 2; BD, bipolar disorder; BDNF, brain-derived neurotrophic factor; CaMKII, calcium/calmodulin-dependent protein kinase II; cAMP, cyclic adenosine monophosphate; CREB, cAMP response element binding protein; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; FDA, Food and Drug Administration; GDNF, glial cell line-derived neurotrophic factor; GSK3, glycogen synthase kinase-3; GWAS, genome-wide association studies; HD, Huntington disease; I-2, protein phosphatase-1/inhibitor-2 complex; IGF, insulin-like growth factor; IL, interleukin; IMPase, inositol monophosphatase; IP3, inositol 1, 4,5-triphosphate; iSPC, induced pluripotent stem cell; MDD, major depressive disorder; miRNA, microRNA; mTOR, mammalian target of rapamycin; NCS-1, neuronal calcium sensor protein 1; NF- κ B, nuclear factor κ -light-chain-enhancer of activated B cells; NMDAR, N-methyl-D-aspartate receptor; PD, Parkinson disease; PGM, phosphoglucomutase; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; PP1, protein phosphatase 1; PRS, polygenic risk score; SNP, single nucleotide polymorphism; STAT, signal transducer and activator of transcription; TBI, traumatic brain injury; TLR4, Toll-like receptor 4; TrkB, tropomyosin receptor kinase B; UPR, unfolded protein response.

I. Introduction

Lithium is an element of the alkali-metal group with an atomic weight of 6.94 (de Laeter et al., 2003). Lithium salts, which include lithium cation, lithium citrate, lithium carbonate, and lithium sulfate, possess mood-stabilizing properties and have been used for the treatment of manic-depressive illness ever since John Cade's discovery in the mid-20th century (Shorter, 2009). Lithium was officially approved to treat acute manic episodes by the US Food and Drug Administration (FDA) in 1970 and affective recurrences in 1974 after more than 30 years of recollected clinical evidence on its efficacy (Cade, 1949; Gershon, 1970; Davis and Fann, 1971). However, its pharmaceutical promotion was initially discouraged due to its low price and unpatentability, along with the potential for serious adverse effects (McKnight et al., 2012; Rybakowski et al., 2022) that limited lithium's commercial appeal and uptake. Despite its demonstrated clinical efficacy, lithium's use has witnessed a considerable decline in recent years (Rhee et al., 2020; Carvalho et al., 2021; Bauer, 2022), concurrently with the discovery and marketing of second-generation antipsychotics for the treatment of bipolar disorder (BD) (Yatham, 2005), that proved equal efficacy in the management of acute manic episodes (Segal et al., 1998; Berk et al., 1999).

The FDA-labeled indications of lithium are limited to the maintenance treatment of BD as well as the treatment of acute manic episodes in BD; however, its use is not limited to these conditions. Lithium is mainly used for the prophylaxis of recurrence and in the acute treatment of manic, hypomanic, and depressive episodes in patients with BD (Carvalho et al., 2014; Malhi et al., 2015; Fountoulakis et al., 2017; Verdolini et al., 2021; Nestsiarovich et al., 2022), although its efficacy may be greater preventing mania than depression when considering its polarity index (Popovic et al., 2012; Carvalho et al., 2014; Vieta et al., 2018). Lithium is additionally employed as an adjunctive treatment, augmenting the effect of antidepressants in individuals diagnosed with major depressive disorder (MDD) (Undurraga et al., 2019). Evidence from many observational studies and randomized controlled trials also supports the antisuicidal effect of lithium (Cipriani et al., 2013). Because of its narrow therapeutic index (approximately 2), regular plasma monitoring of lithium concentration is essential. It should be administered to reach a concentration of 0.5–1 mEq/L 10–14 hours after the last administration (Malhi et al., 2020). Many patients with BD show an excellent response to lithium; however, the response may vary among patients (Kessing et al., 2011; Fornaro et al., 2016a; Hui et al., 2019; Lin et al., 2021; Stone et al., 2021).

Even though lithium is commonly employed in clinical practice and is acknowledged for its effectiveness in treating BD, the mechanism through which it produces its effects remains largely unclear. The intricate impacts

of lithium can be investigated across various levels, encompassing cellular and intracellular neuronal alterations, neural networks, and neurocognition. As a result, the clinical response to this treatment may vary, leading to a heterogeneous outcome (Ikonomov and Manji, 1999; Pasquali et al., 2010; Frelaud and Beaulieu, 2012; Forlenza et al., 2014; Akkouch et al., 2020; Puglisi-Allegra et al., 2021). The etiology of BD remains incompletely understood, thought to arise from an intricate interplay of elements that involve abnormalities in neuroanatomical structure and function, disrupted signaling pathways and gene expression, impaired synaptic plasticity, and decreased brain cell density (Carvalho et al., 2020). Additionally, lithium's neurotrophic effects have been suggested to potentially mitigate some of these impairments (Puglisi-Allegra et al., 2021). Recent advances in genetics and bioinformatics illuminate lithium's pharmacology and have renewed the interest in its mechanism (Hou et al., 2016; Cearns et al., 2022), together with a rediscovery of lithium in clinical practice (Anmella et al., 2021).

This review will delve into the contemporary understanding and recent advancements concerning lithium's biologic functions and its roles in various brain disorders. To be precise, we start with a perspective on the clinical use of lithium in mood disorders. Next, we discuss its molecular mechanisms and physiologic roles in cellular processes, broadening the perspective on new potential biologic underpinnings related to different clinical uses of lithium. Moreover, we present limitations to the use of lithium through the explication of mechanisms implied in its toxicity, and we conclude our review with new perspectives and future directions in lithium treatment and research.

II. Clinical Use in Mood Disorders

BD is a severe psychiatric disorder characterized by recurring mood episodes of depression alternating with episodes of euphoria (called manic/hypomanic episodes), affecting approximately 2% of the general population (Vieta et al., 2018). Despite the pharmacological guidelines for treatment being well established, most individuals still experience high rates of mood recurrences or significant residual symptoms while on medication (Perlis et al., 2006). Lithium is considered a gold standard in treating all phases of BD, and it is recommended in all different international treatment guidelines (Fountoulakis et al., 2017; Malhi et al., 2020; Yatham et al., 2018). The targeted lithium level, also known as the therapeutic range, is the desired concentration of lithium in the blood to achieve optimal treatment outcomes in individuals with BD. The specific targeted lithium levels can vary among countries and guidelines. For example, the American Psychiatric Association (Hirschfeld et al., 2003) or the Canadian Network for Mood and Anxiety Treatments and International

Society for Bipolar Disorders guidelines (Yatham et al., 2018) recommend a range of 0.8–1.2 mEq/L for acute mania and 0.6–1.0 mEq/L for maintenance treatment. Similarly, the National Institute for Health and Care Excellence [National Collaborating Centre for Mental Health (UK), 2014] in the United Kingdom suggests a range of 0.8–1.0 mEq/L for acute mania and 0.4–1.0 mEq/L for maintenance treatment. Monitoring lithium levels and adhering to the recommended ranges are essential to ensure the effectiveness of treatment and minimize the risk of side effects. Several guidelines also recommend the use of lithium for treating patients with MDD or individuals with a high risk of suicidality (Kennedy et al., 2016). In addition to its effectiveness in managing and preventing mood disorder symptoms, there is a belief that lithium has the potential to induce neurotrophic and neuroprotective effects across a diverse array of cellular pathways. Moreover, it may impact brain circuits associated with behavioral, cognitive, and motor-related functions (Puglisi-Allegra et al., 2021). Indeed, it has been recently reported that lithium might exert neuroprotection in stroke (Chen et al., 2022b), neurodegenerative diseases such as dementia (Forlenza et al., 2014; Morris and Berk, 2016; Velosa et al., 2020), spinal cord injury (Yang et al., 2012), and other diseases involving the nervous system, including BD (Bauer et al., 2003). Indeed, the number of lifetime affective episodes in BD might result in biologic insult, ultimately worsening the course of the illness, which is conceptualized as “neuroprogression.” For these reasons, lithium’s clinical use and neuroprotective effect should be seen as intertwined entities since lithium might prevent neuroprogression, and advanced neuroprogression might impact lithium’s clinical response in BD (Bauer et al., 2017).

A. Acute Mania

A manic episode is marked by elevated or irritable mood, increased energy levels, reduced need for sleep, and diminished attention span, among other symptoms that may include aggressive behavior and impulsiveness. Lithium is one of the indicated first-line treatments for acute mania. It has proven to be more effective than placebo and equal to other mood stabilizers or antipsychotics in several studies (Cipriani et al., 2011; Hayes et al., 2016; Bohlken et al., 2021). In addition, a recent meta-analysis including 36 randomized controlled trials showed that lithium was more effective than placebo at inducing response (odds ratio, 2.13; 95% CI, 1.73–2.63) or remission (odds ratio, 2.16; 95% CI, 1.73–2.69) in acute mania (McKnight et al., 2019). However, it is often administered as a combination therapy with atypical antipsychotics, (e.g., olanzapine, aripiprazole, cariprazine, and asenapine, among others) (Conus et al., 2015; Kishi et al., 2022) to treat concomitant acute agitation or aggressive behavior during manic states

(Chengappa et al., 2004; de Bartolomeis and Perugi, 2012; Grande and Vieta, 2015, Kishi et al., 2022). Response to lithium appears to be better in patients with classic (euphoric) mania, whereas response rates are relatively worse in mixed states (Swann et al., 1997; Sportiche et al., 2017; Grunze et al., 2018) or rapid cycling (Calabrese et al., 2005). Lithium is primarily used in concentrations in the range of 0.8–1.2 mmol/L during acute mania (Yatham et al., 2018).

B. Acute Depression

Despite the high rates of patients with BD experiencing multiple depressive episodes during their life, with a significant impact on global functioning (Manning, 2005; Undurraga et al., 2012), few pharmacological options exist to treat acute depressive episodes (Nivoli et al., 2011; Vieta and Valenti, 2013; Correia-Melo et al., 2017). Lithium is not approved for treating depressive episodes for bipolar type I or type II patients since evidence of its efficacy on acute depressive episodes in monotherapy is less robust than that in acute manic episodes (Manchia et al., 2019; Rakofsky et al., 2022). Indeed, a recent meta-analysis showed no statistically significant differences between lithium versus antidepressants or placebo in patients with bipolar depression (Rakofsky et al., 2022). It should be noted that lithium might be the most studied drug in BD. Still, its effect on acute bipolar depression remains underexplored, with most studies having several methodological limitations (Fountoulakis et al., 2022). Nevertheless, the use of lithium for the treatment of acute bipolar depressive episodes is every day and is also supported by clinical guidelines for its antisuicidal properties and prophylactic effect against affective recurrences, especially in combination with other agents (Malhi et al., 2020).

Despite not being the first-line option, lithium is also prescribed to treat acute depression in patients with MDD, often as adjunctive treatment to conventional antidepressants (Undurraga et al., 2019). Lithium monotherapy did not show superiority over citalopram in unipolar depressed patients (Bschor et al., 2013) and is not an established treatment of acute major depression. Two studies showed that lithium is superior to antidepressants (Bauer et al., 2000) or electroconvulsive therapy (Lambrichts et al., 2021) in preventing relapses in MDD, but these results should be replicated in larger samples. Lithium’s role as an augmentation of antidepressants in treatment-resistant major depressive episodes is well clinically established and proven in several clinical trials (Dold et al., 2018; Vázquez et al., 2021).

C. Maintenance and Prophylaxis of Mood Episodes in Bipolar Disorder

The maintenance treatment of BD represents a major clinical challenge since the lifetime recurrence rate of

affective episodes of both polarities is 95%, with a major impact on long-term disability and quality of life (Perlis et al., 2006; Vázquez et al., 2015; Etain et al., 2021). Noteworthy, people with BD experience depression more frequently than they experience mania or hypomania (Kupka et al., 2007). This may encourage the use of lithium in real-world clinical practice beyond the sole FDA approval, also aiming at reducing the odds of polypharmacy in BD (Fornaro et al., 2016b). Lithium continues to be the preferred choice for maintenance treatment in both types I and II of BD (Hayes et al., 2016; Kessing, 2019). A network meta-analysis comparing the efficacy and tolerability of various pharmacological treatments for bipolar disorder maintenance therapy demonstrated that lithium was more effective than a placebo in preventing mood relapses (Kishi et al., 2021). Furthermore, in a multicenter, randomized, open-label trial involving individuals with BD type I, it was found that both combination therapy with lithium and valproate, as well as lithium monotherapy, were more effective at preventing relapses compared with valproate monotherapy (Geddes et al., 2010). In general, combination therapy with lithium proved superior to mood-stabilizer monotherapy in preventing recurrence of any type for up to 12 months (Kishi et al., 2021).

Among other mood stabilizers, lithium also demonstrated a higher preventive effect for manic episodes compared with depressive episodes (Nestsiarovich et al., 2022). In the long-term treatment of BD, target serum levels should generally be around 0.6–1 mmol/L to reach optimal clinical efficacy. There has been a recent proposal suggesting a dose-response relationship in which higher serum lithium levels are associated with a reduced risk of recurrence (Hsu et al., 2022).

D. Antisuioidal Effect

Lithium has been associated with reduced suicide risk in individuals with BD or MDD as well as in the general population in diverse observational and randomized clinical trials (Cipriani et al., 2013). The reduction of suicide risk is up to 60% after long-term lithium treatment. A rebound effect with increased rates of suicide with lithium discontinuation or in patients with poor treatment adherence has also been reported (Gonzalez-Pinto et al., 2006). Lithium concentrations in drinking water might also influence suicide risk, although the evidence is controversial (Del Matto et al., 2020; Rybakowski, 2022). In the Systematic Treatment Enhancement Program for Bipolar Disorder study, the presence of suicidal ideation was found to be similar among patients with BD receiving lithium treatment and those not receiving it (Goldberg and Chengappa, 2009). Moreover, the study revealed no significant relationship between lithium use and suicide attempts or completions as well as for other mood-stabilizing medications (Marangell et al., 2008). Interestingly, one recent randomized clinical

trial reported no significant difference between lithium and placebo in preventing suicide among veterans (Katz et al., 2022). However, this study reported off-therapeutic ranges of lithium levels (between 0.54 and 0.46 mmol/L) and had other critical methodological limitations (Manchia et al., 2022). Contrasting results about the antisuioidal effect of lithium have been reported recently (Nabi et al., 2022), but the reasons for the discrepancy between these findings and previous meta-analyses may depend on the seemingly arbitrary inclusion and exclusion of randomized controlled trials and an unsatisfactory reinterpretation of data compared with the original publications (Bschor et al. 2022). The putative mechanism by which lithium exerts its antisuioidal effect is mainly attributed to the mood-stabilizing properties in patients with mood disorders but also to some of its intrinsic characteristics in reducing impulsive or aggressive behavior (Müller-Oerlinghausen and Lewitzka, 2010).

E. Neuroprotective and Neurotrophic Effects of Lithium

Extensive evidence shows that lithium exerts a neuroprotective effect through several biologic mechanisms. These include the reduction of oxidative stress and inflammation, up-regulation of mitochondrial function, and activation of neurotrophic response (Diniz, et al., 2013; Rybakowski et al., 2018). BD is a chronic disease characterized by recurrent affective episodes associated with related structural, functional, and the aforementioned neurochemical brain changes in an illness-related process conceptualized as “neuroprogression” (Berk, 2009). The biologic underpinnings of BD neuroprogression are thought to include different pathways, encompassing regulation of neurogenesis and apoptosis to inflammation and redox stress-related pathways and epigenetic modifications (Berk, 2009). The changes affecting brain structure and function differ from those observed at the onset of the disease and become more evident with illness’ chronicity, which is linked to a high number of depressive or manic episodes. Indeed, the neuroprogression construct suggests that each mood episode might cause a biologic insult and consequent neural damage, therefore increasing brain vulnerability to developing future illness episodes (Berk, 2009).

Neuroprogression influences the prognosis of BD, linked to a poorer response to treatment, including lithium (Fico et al., 2021), atypical antipsychotics (Berk et al., 2011) and psychotherapy, cognitive and functional decline, and a higher tendency to relapse (Bauer et al., 2017). However, neuroprogression is probably only evident in a subgroup of patients with BD (Martino et al., 2017). Because of the progressive nature of BD, it is essential to commence disease-modifying treatments as early as possible. Lithium has been shown to prevent structural and cognitive change after the first episode of mania (Berk et al., 2017; Daglas et al., 2017). Indeed, good lithium responders also seem to show lower levels

of deterioration during follow-up (Berghöfer et al., 2013). Thus, lithium's unique neuroprotective properties might be key in targeting neurobiological alterations during neuroprogression in BD (Rybakowski and Suwalska, 2010; Squassina et al., 2017; Vecchio et al., 2020) as well as in other neurodegenerative diseases (Forlenza et al., 2014). Lithium's neuroprotective effect may be reflected in increased cerebral gray matter in healthy subjects and patients with BD (Moore et al., 2000; Berk et al., 2017; Hozer et al., 2021). Also, lithium might ameliorate cellular signal transduction pathways, mood regulation, and neurocognitive function in BD (Puglisi-Allegra et al., 2021). Whether the proposed preventive effects of lithium are exerted on the systems mentioned above to prevent changes and, thus, cognitive decline in BD is unknown to date.

A better understanding of lithium's impact on neuroprogression and its underlying biologic pathways affecting mood regulation and neurocognitive functions might help to disentangle the etiology of BD.

III. Mechanism of action

A. Inositol Monophosphatase, Posphoglucomutase, and Glycogen Synthase Kinase-3 Inhibition

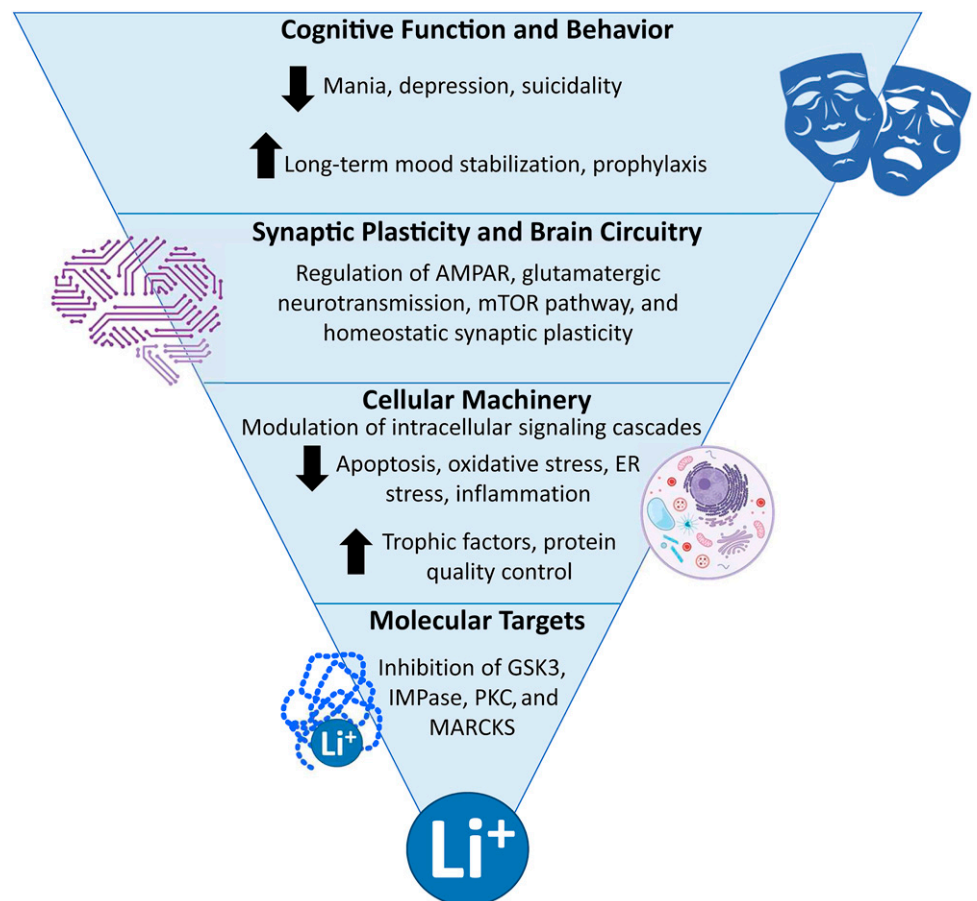
The therapeutic and mood-stabilizing effects of lithium are thought to involve neurotrophic and neuroprotective

mechanisms (Malhi et al., 2013; Malhi and Outhred, 2016; Won and Kim, 2017). Lithium is pleiotropic, and it regulates a variety of proteins/cellular regulatory pathways impacting different structural and functional levels of the brain, from molecular and cellular elements to synaptic plasticity, neurotransmission, and brain circuits. Hence, it is unclear if the agent has a single mechanism of action or works through a combination of synergistic mechanisms (Fig. 1) (Alda, 2015; Anand et al., 2020; Kavalali and Monteggia, 2020; Haggarty et al., 2021; Ochoa, 2022).

Earlier studies have highlighted the primary criteria for confirming the direct molecular targets of lithium, which include 1) the inhibition of the target protein's activity at lithium concentrations that are therapeutically significant (0.62–1.2 mM) both in vitro and in vivo procedures, 2) comparable outcomes by employing inhibitors of the suggested target that are chemically distinct from lithium, 3) that the mimicking of lithium's effect is achieved by impairing the function of the proposed target gene, and 4) restoring of target function or a downstream effector that reverses the effect of lithium (Phiel and Klein, 2001; O'Brien et al., 2011).

Specific lithium targets have been identified, including enzymes such as inositol monophosphatase (IMPase) and magnesium-dependent phosphomonoesterases, which are

Fig. 1. Lithium (Li^+) modulates a number of cellular pathways in the brain involved in neuroplasticity and neuroprotection. Inhibition of GSK3 is clearly central to its therapeutic mechanisms. Recent research has elucidated the direct and indirect effects of lithium on neurotrophic response, ER stress, UPR, autophagy, oxidative stress, inflammation, and mitochondrial function, mechanisms modulated by lithium that facilitate cell viability. Lithium elicits homeostatic synaptic plasticity that is dependent on AMPAR expression on the cell surface and requires BDNF/TrkB signaling. Structural imaging studies indicate that lithium may lead to neuroprotection by increasing gray matter volumes in the amygdala, hippocampus, and prefrontal cortex. Conversely, findings from neuropsychological and functional magnetic resonance imaging studies suggest that the overall influence of lithium on cognition leans toward potential cognitive impairment. Different biologic pathways might be targeted during affective episodes: neurotransmitter modulation, inhibition of GSK-3 and dopamine regulation in mania, enhancement of neuroplasticity and neurotransmitter modulation in depression and cAMP signaling, and glutamate and GABA regulation during maintenance phases. MARCKS, myristoylated alanine-rich C kinase substrate.



structurally related (Hallcher and Sherman, 1980). These enzymes, which encompass inositol polyphosphate 1-phosphatase (IPPase), fructose 1,6-bisphosphatase (FBPase), and bisphosphate 3'-nucleotidases (BPntase), possess a shared metal ion-binding consensus sequence. Additionally, phosphoglucomutase (PGM), responsible for converting glucose-1-phosphate (G1P) to glucose-6-phosphate (G6P), requires magnesium and is directly inhibited by lithium (York et al., 1995, 2001; Phiel and Klein, 2001). Additionally, lithium directly inhibits glycogen synthase kinase-3 (GSK3), a crucial enzyme in glycogen metabolism that is now known to regulate various cell functions (Klein and Melton, 1996; Cohen and Frame, 2001; Beurel et al., 2015).

Despite their structural differences, all three classes of lithium targets—IMPase, PGM, and GSK3—rely on magnesium for their function. In each instance, lithium competes to occupy a magnesium-binding site (Snitow et al., 2021). It is noteworthy that the identified primary targets of lithium are intricately linked to the regulation of glucose metabolism or the control of phosphoglucose levels. Specifically, PGM catalyzes the isomerization of G6P to G1P, IMPase plays a crucial role in gluconeogenesis, and GSK3 acts to inhibit the incorporation of glucose into glycogen.

Indeed, the risk of type 2 diabetes is up to 3 times higher in patients with BD than in healthy controls of similar age and sex. Over half of BD patients have impaired glucose metabolism, including insulin resistance, impaired glucose tolerance, or type 2 diabetes (Calkin et al., 2015; Vancampfort et al., 2016; Giménez-Palomo et al., 2022). Interestingly, improvement in insulin resistance with metformin is associated with improved symptoms of BD (Calkin et al., 2022). Furthermore, lithium treatment also affects downstream effectors, including adenylate cyclase, the phosphoinositol cascade, and the metabolism of arachidonic acid. (Gould et al., 2004; Quiroz et al., 2004; Rao and Rapoport, 2009; Chiu et al., 2013). Since lithium affects other magnesium-dependent proteins, it has been estimated that there are >3000 human proteins whose function may be modified by lithium treatment (Davies et al., 2000; Piovesan et al., 2012; Puglisi-Allegra et al., 2021). Lithium's capacity to interact with a wide range of molecules grants it significant potency as a pharmacological tool and makes it a valuable asset in both clinical and preclinical research (Fig. 2).

GSK3 is a serine/threonine protein kinase (PK) with two isoforms, GSK3 α and GSK3 β . Although both isoforms are expressed at comparable levels in the mouse brain (Yao et al., 2002), in the human brain, the β isozyme predominates (Lau et al., 1999), highlighting its critical role in the functioning of the human central nervous system. Furthermore, GSK3 plays a pivotal role in numerous cellular processes and diseases (Harwood, 2001; Jope and Johnson, 2004; Beurel et al., 2015).

Several mechanisms are involved in the control of GSK3 actions, including phosphorylation, protein complex formation, and subcellular distribution. In addition, GSK3 has many unique properties, such as constitutive activity in cells and inhibition by extracellular stimuli, unlike other kinases, that are usually activated by extracellular stimuli. Phosphorylation on a serine residue of N-terminal GSK3 (serine 21 in GSK3 α and serine 9 in GSK3 β) leads to activity inhibition of GSK3. There are several protein kinases, including serine/threonine kinase (Akt; previously known as protein kinase B), protein kinase A, and protein kinase C (PKC), known to phosphorylate GSK3 to inhibit its function (Fang et al., 2000). GSK3 activity is also negatively regulated through growth factor stimulation of mitogen-activated protein kinases (MAPKs) and mammalian target of rapamycin (mTOR) (Doble and Woodgett, 2003; Kirshenboim et al., 2004).

GSK3 maintains cellular homeostasis by interacting with numerous substrates, such as transcription factors, glycolytic enzymes, pro- and antiapoptotic factors, mitochondrial channels, membrane receptors, and cytoskeleton-associated proteins (Duda et al., 2018). The dysregulation of GSK3 is associated with numerous prevalent and frequently comorbid diseases, such as diabetes and/or insulin resistance, Alzheimer disease (AD), Parkinson disease (PD), schizophrenia, MDD and BD, among others (Jope and Johnson, 2004; Beurel et al., 2015). Studies in human post mortem brain and peripheral cells have identified correlations between alterations in GSK3 function and mood regulation, suggesting that depression may be associated with impaired inhibitory control of GSK3, and mania with GSK3 hyperactivity (Karege et al., 2007; Diniz et al., 2011; Jope, 2011; Iwahashi et al., 2014).

Consequently, a decline in serine phosphorylation of GSK3 was observed in peripheral blood mononuclear cells during the disease state, and its levels were found to rise following lithium therapy (Li et al., 2010). Additionally, recent evidence indicates that BD exhibits a bimodal pattern of energy, with enhanced energy levels during manic episodes and decreased energy levels during depressive episodes. Notably, individuals experiencing mania demonstrate heightened mitochondrial respiration and ATP production as opposed to individuals during euthymia or depression, who display diminished mitochondrial function (Morris et al., 2017).

The notion that GSK3 represents the therapeutic target of lithium is reinforced by preclinical research involving genetic modifications of GSK3 or its downstream components. Downregulation of GSK3 β mimics the effects of lithium on behavior in mice, whereas GSK3 β overexpression reverts the lithium-induced neurobehavioral effects in mice (O'Brien et al., 2004, 2011), indicating that GSK3 is a critical target of lithium in mammalian behaviors. Moreover, in β -arrestin

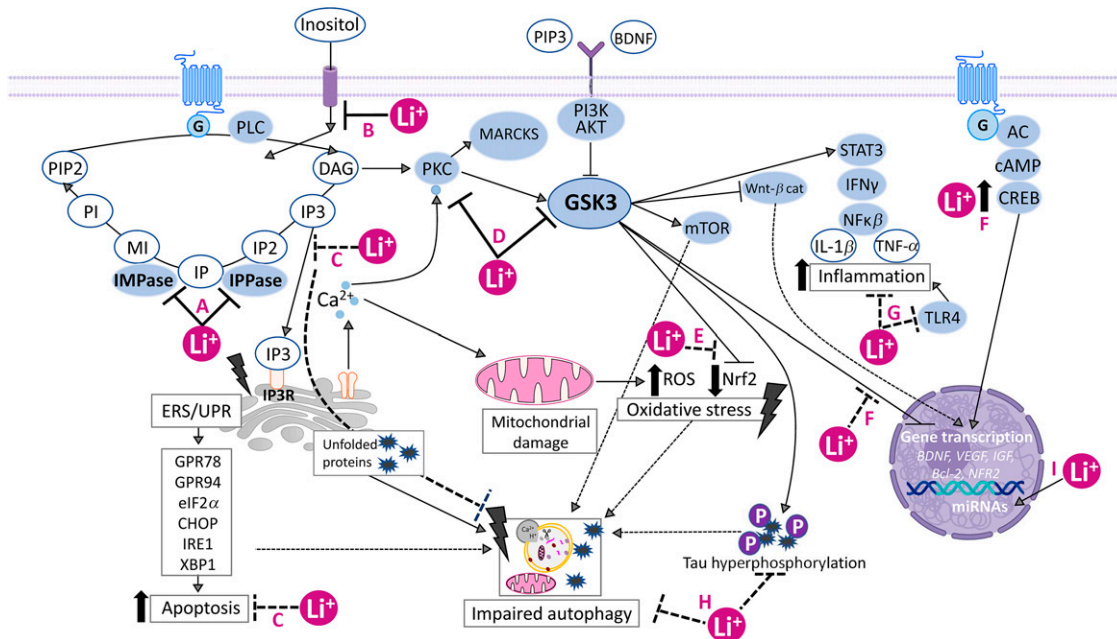


Fig. 2. Representative scheme of the main molecular and cellular targets modulated directly and indirectly by lithium (Li^+). Lithium inhibits IMPase (A), including inositol polyphosphate 1-phosphatase (IPPase), fructose 1,6-bisphosphatase (FBPase), and bisphosphate nucleotidases (BPntase). These enzymes are part of the phosphatidylinositol 4,5-bisphosphate (PIP₂) cycle, one of the signaling pathways underlying many cellular functions, such as G-coupled neurotransmitter receptors (GPCR) signaling, cytokinesis, endocytosis, and apoptosis. Phospholipase C (PLC) mediates the hydrolysis of PIP₂ to the secondary messengers diacylglycerol (DAG) and IP₃, which, in turn, activate downstream signaling pathways, including PKC and IP₃ receptor (IP₃R)/ER stress/UPR. Therefore, lithium inhibits ER stress (ERS), altered UPR signaling, and increased intracellular Ca^{2+} levels through depletion of free inositol (B) and subsequent lower IP₃ levels and IP₃R activation (C). ERS and abnormal UPR result in the buildup of misfolded or unfolded proteins, faulty autophagy, and cell death via apoptosis. Lithium acts to counter these effects through the IP₃/IP₃R mechanism (C). Lithium directly inhibits GSK3 and facilitates the phosphorylation of GSK3 at the N-terminal serine (D). Lithium also acts by inhibiting PKC (D) through an intricate myristoylated alanine-rich C kinase substrate (MARCKS) pathway initiated by its inhibition of GSK3 (D). Inhibition of PKC and GSK3 by lithium prevents the potentially harmful effects of downstream activation of these pathways. These include 1) oxidative stress pathway (E) due to accumulation of reactive oxygen species (ROS) scavenged from damaged mitochondria and downregulation of the transcriptional nuclear factor (erythroid-derived 2)-like 2 (Nrf2); 2) impaired transcription of neurotrophic, neuroprotective, and antioxidant genes (F), such as BDNF, vascular endothelial growth neurotrophic (VEGF), IGF, Bcl-2, and Nrf2, which is reversed by lithium through inhibition of GSK3 (D) and activation of the CREB transcription factor placed downstream of GPCRs (F); 3) activation of the inflammasome, production of proinflammatory cytokines underlying activation of the STAT/interferon- γ (INF γ)/NF- κ B pathway (G); and 4) accumulation of hyperphosphorylated τ , which is concurrent to cytoskeletal alterations and autophagy impairment (H). The anti-inflammatory effects of lithium are also produced by suppressing TLR4 signaling (G). Lithium also modifies the expression of miRNAs and their targeted mRNA, suggesting that they could play a role in modulating lithium's clinical efficacy (I). Modified from Puglisi-Allegra et al. (2021). eIF2 α , eukaryotic translation initiation factor 2 α .

2 knockout mice, lithium administration fails to impact Akt/GSK3 signaling but still induces behavioral changes associated with GSK3 inhibition, resembling the effects observed in wild-type mice. Correspondingly, specific GSK3 inhibitory peptides reproduce the behavioral outcomes of lithium in mice (Gould et al., 2004; Kaidanovich-Beilin et al., 2004; Beaulieu et al., 2004, 2008). Thus, lithium inhibits GSK3 signaling by binding directly to the magnesium-sensitive site of the enzyme and indirectly by increasing the phosphorylation of this kinase at specific serine21/9 residues. Valproate, in addition to antidepressants (including the rapid-acting antidepressant ketamine) and antipsychotics, indirectly suppresses GSK3 activity through the phosphorylation of serine21/9. This suggests a common mechanism involving GSK3 across these treatments (Beurel et al., 2011; Zarate and Machado-Vieira, 2016; Snitow et al., 2021). Nevertheless, a recent study using selective GSK3 β inhibitors, such as AZ1080 and compound A, showed that GSK3 β inhibition alone does not replicate the lithium-induced behavioral

and cellular effects in rats (Georgievska et al., 2013). Additionally, GSK3 β inhibition alone did not increase brain-derived neurotrophic factor (BDNF) levels. In contrast, lithium administration did (Caberlotto et al., 2013), indicating that other mechanisms/pathways may be involved in the therapeutic responses to lithium (Fig. 2).

However, the mechanisms underlying GSK3 lithium-induced inhibition and how it contributes to both anti-manic and antidepressant effects remain uncertain. Recent research suggests that mood stabilizers work by blocking GSK3, which, in turn, makes cells more responsive to natural extracellular signals, like neurotrophins and neurotransmitters. These signals typically activate Akt, leading to the phosphorylation and deactivation of GSK3 inactivation (Puglisi-Allegra et al., 2021; Snitow et al., 2021) (Fig. 3). However, GSK3 opposes its phosphorylation through two mechanisms: one involving the inhibition of Akt through a β -arrestin complex and the other involving the activation of protein phosphatase 1 (PP1) by GSK3, which is inhibited by protein

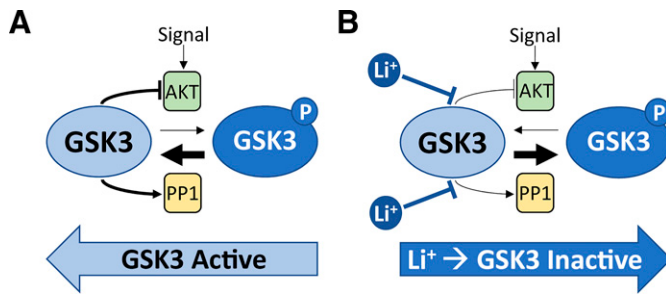


Fig. 3. Positive feedback mechanisms regulating GSK3. (A) GSK3 is phosphorylated and inhibited by AKT in response to upstream signals. PP1 dephosphorylates and activates GSK3. GSK-3 inhibits AKT and activates PP1, thereby potentiating its activity. (B) Lithium, directly and indirectly, inhibits GSK3 and disrupts both feedback loops. Disruption of these feedback loops by lithium may leave an increased response of endogenous ligands (e.g., neurotransmitters such as glutamate, dopamine, and serotonin) that signal through AKT and whose synaptic levels are affected in BD. Modified from Snitow et al. (2021).

phosphatase-1/inhibitor-2 complex (I-2). Deactivation of Akt hinders the phosphorylation and suppression of GSK3. Lithium and other GSK3 inhibitors interfere with this process by disrupting the complex, enabling Akt to stay active and continue phosphorylating GSK3 (Beaulieu et al., 2004; O'Brien et al., 2011). The phosphorylation of GSK3 at I-2 prompts its detachment from PP1, which subsequently leads to the dephosphorylation of GSK-3 and the restoration of its activity. Lithium and other GSK3 inhibitors block the process by which PP1 dephosphorylates GSK3 in an I-2-dependent manner (Zhang et al., 2003; Freland and Beaulieu, 2012; Snitow et al., 2021).

As a result, when GSK3 is pharmacologically inhibited, it lowers the threshold for endogenous signals to deactivate cellular GSK3 clusters. This means that even relatively weak signals can generate a consistent response due to the increased inhibition of GSK3. This mechanism may explain how lithium sensitizes cells to endogenous neurotransmitters or other signals that may be diminished in BD, and it may account for the effectiveness of lithium treatment as an adjunct to antidepressants in treatment-resistant depression (Snitow et al., 2021).

Lithium shows efficacy in treating both manic and depressive episodes in BD and is a potential drug for neurodegenerative diseases. Unfortunately, lithium suffers from significant drawbacks, mainly a narrow therapeutic window and renal toxicity (Davis et al., 2018). Undoubtedly, among the many molecular targets of lithium, GSK3 β may be in part responsible for its therapeutic effects, so the development of selective inhibitors of this kinase could influence the side effects of lithium. Although beyond the scope of this review, in recent years, the application of machine learning is accelerating the discovery of potential drugs with GSK3 β inhibitory activity that can be repurposed as therapeutics for mood disorders and/or neurodegenerative disorders

[see Kleandrova and Speck-Planche (2020), Vignaux et al. (2020), Zhu et al. (2020), and Reilley et al. (2021) for more details].

B. Protein Kinase C and Myristoylated Alanine-Rich C Kinase Substrate Inhibition

PKC is a family of enzymes involved in mood regulation, relying on calcium and phospholipids for activation. The conventional PKC isoforms (α , β I, β II, γ) necessitate both calcium and diacylglycerol for activation, whereas the newer PKC isoforms (δ , ϵ , η , θ , μ) can be activated solely by diacylglycerol (Zarate and Manji, 2009). The conventional PKC isoforms are the prevailing variants and are prominently present in multiple brain regions, with a notable presence at presynaptic terminals, including those in the prefrontal cortex, amygdala, and hippocampus (Naik et al., 2000; Zarate and Manji, 2009). PKC signaling is involved in several intracellular pathways regulating neuronal excitability, neurotransmitter release, glutamate signaling, and neuroplasticity (Zarate et al., 2003, 2006a; Chu et al., 2014; Pahl et al., 2014) and underlies many of the pathologic mechanisms, including neuroinflammation and mitochondrial dysfunction related to oxidative stress and apoptosis (Jun et al., 2014; Nam et al., 2015).

Accumulating evidence from both human and animal studies strongly supports the substantial role played by this enzyme group in BD. Inhibiting PKC has been shown to effectively reduce manic-like behaviors and mitigate hippocampal cell degeneration in rat models of mania induced by sleep deprivation (Abrial et al., 2013). Individuals with BD show increased PKC activity in both central (cortical) and peripheral (platelet) regions when compared with healthy controls (Wang and Friedman 1996; Wang et al., 1999). Finally, a meta-analysis involving 8700 patients with unipolar and bipolar depression has identified a significant correlation between PKC ϵ genetic locus and suicidality (Saxena et al., 2017). Furthermore, genomic investigations have established correlations between specific loci and lithium responsiveness, indicating a potential shared genetic predisposition for both the disease and the response to treatment (Turecki et al., 2001; Khayachi et al., 2021). In this context, research has shown that long-term lithium treatment leads to a reduction in PKC levels in the platelets of individuals with BD (Soares et al., 2000). Additionally, both lithium and valproic acid have shown the ability to inhibit PKC activity in vitro and in vivo (Chen et al., 1994, 2000a; Zarate and Manji 2009), which has led to the study of PKC as a potential therapeutic drug target.

Remarkably, the prolonged use of quercetin, which is a nonspecific PKC inhibitor, has been observed to block methylphenidate-induced hyperlocomotion and lipid peroxidation in mice (Kanazawa et al., 2017). Furthermore, tamoxifen, another potent PKC inhibitor, has shown efficacy in the treatment of acute manic or mixed episodes

in BD (Yildiz et al., 2008, 2016; Amrollahi et al., 2011; Kulkarni et al., 2014; Talaei et al., 2016). It is worth noting that despite its promising antimanic properties (Talaei et al., 2016; Palacios et al., 2019; Novick et al., 2020), the FDA has not granted its approval for the treatment of manic episodes. However, a new PKC inhibitor called endoxifen has received approval in India (Ahmad et al., 2021).

C. Enhancement of Trophic Factors

Putative mechanisms for the therapeutic effects of lithium also include the upregulation of trophic factors and activation of their receptors (Hashimoto et al., 2004; Seelan et al., 2008; Gideons et al., 2017; Haupt et al., 2021). In addition to being the first choice in the treatment of BD, recent reports point to lithium having beneficial effects on Alzheimer disease (Nelson et al., 2014; Damri et al., 2020), and there are suggestions that lithium may help individuals with PD (Guttuso et al., 2019). At least part of the reason that lithium has benefits in these pathologic conditions is probably due to its effects on BDNF levels.

BDNF, acting via the tropomyosin receptor kinase B (TrkB) receptor to promote cortical development, synaptic plasticity, neurogenesis, and neuronal viability, is recognized for its significant contribution to BD and other psychiatric disorders (Fernandes et al., 2011; Autry and Monteggia, 2012; Malhi et al., 2013; Scola and Andreazza, 2015; Rowland et al., 2018). Six separate meta-analyses consistently demonstrated that in BD, BDNF plasma levels were significantly lower than those in healthy controls, schizophrenia, or unipolar depression (Molendijk et al., 2014; Fernandes et al., 2015; Rowland et al., 2018). Moreover, BDNF levels are reduced in mania or depression but not during euthymia (Tunca et al., 2014; Fernandes et al., 2015; Rowland et al., 2018). Furthermore, in individuals with BD, BDNF mRNA levels in white blood cells are also lower in individuals with BD compared with unaffected individuals (D'Addario et al., 2012). Post mortem analysis of hippocampal tissue has also revealed reduced BDNF protein levels in patients with BD (Knable et al., 2004). Manic (Frey et al., 2006; Jornada et al., 2010; Fries et al., 2015) and depressive-like behavioral animal models (Tsankova et al., 2006; Björkholm and Monteggia, 2016; Koo et al., 2019) have also shown a decrease in both BDNF mRNA and protein levels in the hippocampus. Conversely, lithium treatment has been associated with increased BDNF protein levels (Cunha et al., 2006; Tramontina et al., 2009; de Sousa et al., 2011) and increased BDNF mRNA and protein expression in the hippocampus, cortex, and amygdala in rodent models and in cultured cortical neurons (Fukumoto et al., 2001; Yasuda et al., 2009; Jornada et al., 2010). Lithium treatment also increases TrkB activity in neuronal cultures and enhances BDNF-TrkB signaling (Hashimoto et al., 2002).

The potential mechanisms for how lithium increases BDNF levels are complex. Lithium affects adenylyl cyclase enzymes, increasing and stabilizing the production of cyclic adenosine monophosphate (cAMP) (Manji and Lenox, 2000). Increased cAMP levels increase protein kinase A activity, an enzyme that phosphorylates and activates numerous other molecules and enzymes, including the transcription factor cAMP response element binding protein (CREB). When activated through phosphorylation, CREB increases BDNF transcription and production (Zheng et al., 2011). Promoter exons are regions of a gene that promote its transcription to produce more of a targeted protein. The BDNF gene has several promoter exons, and studies in animal models suggest that lithium upregulates the function of promoter exon IV. When exposed to therapeutic concentrations of lithium, cultured rat cortical neurons exhibited elevated levels of BDNF mRNA containing exon IV and an enhanced activity of BDNF promoter IV (Yasuda et al., 2009; Dwivedi and Zhang, 2015). Through increased BDNF production, lithium may enhance neurogenesis, nerve cell growth and survival, and neural plasticity. These effects explain at least part of the therapeutic effects seen with its use. More recently, Gideons et al. (2017) have highlighted the necessity of BDNF-TrkB signaling in the lithium-induced antimanic-like response, whereas this mechanism does not appear to be involved in the antidepressant-like effects of lithium. Furthermore, they have identified a direct impact of lithium treatment on the trafficking of α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPA receptors), wherein there is a decrease in the cell surface expression of AMPARs due to a sustained increase in dynamin-mediated AMPAR endocytosis. This process is reliant on the proper functioning of BDNF-TrkB, offering valuable mechanistic insights into the actions of lithium that may underpin its therapeutic efficacy in the treatment of BD. Furthermore, alterations in BDNF levels induced by lithium alone can effectively inhibit the activity of GSK3 β (Machado-Vieira et al., 2009). It's worth noting that BDNF not only acts as a mediator for gene expression linked to synaptic plasticity through PKC signaling (Arevalo and Wu, 2006) but also plays a role as a regulator of PKC itself, influencing BDNF and other neurotrophins' expression (Xu et al., 2013, 2015b). The intricate interplay between these pathways underscores the complex role that neurotrophins play in regulating a wide range of neuronal signaling mechanisms, rendering them significant molecular targets of lithium.

Other trophic factors have been identified as molecular targets of lithium, such as glial cell line-derived neurotrophic factor (GDNF), vascular endothelial growth factor, and insulin-like growth factor (IGF). However, the mechanisms involved are less understood than those of BDNF (Scola and Andreazza, 2015). GDNF levels increase with lithium treatment in astrocyte cultures

(Emamghoreishi et al., 2015). Hence, it is plausible that the neuroprotective benefits of lithium may not be restricted solely to neurons but could also encompass astrocytes. Several findings on the effects of GDNF in BD reveal that different stages of the disorder and pharmacological treatment with lithium may alter GDNF expression in BD. However, there is some controversy about the possibility of considering GDNF as a nonspecific peripheral factor marker that may respond to lithium treatment (Scola and Andreatza, 2015). Lithium may increase vascular endothelial growth factor expression through phosphatidylinositol 3-kinase (PI3K)/GSK3 β -dependent and -independent pathways in brain endothelium and astrocytes, contributing to lithium's ability to promote neurovascular remodeling after stroke (Guo et al., 2009).

Furthermore, genetic investigations have indicated the involvement of IGF in BD as its gene is situated in the chromosomal region 12q23.2, a region associated with BD pathophysiology (Curtis et al., 2003; Pereira et al., 2011). Interestingly, the mRNA expression of IGF-binding protein-2, a protein with high affinity for IGF-1 or IGF-2, used to transport these factors to other tissues or organs, was found to be reduced in the prefrontal cortex of individuals with BD (Bezchlibnyk et al., 2007). Moreover, patients with BD exhibited lower blood levels of IGF-1 compared with those with schizophrenia (Palomino et al., 2013). Intriguingly, IGF-1 was observed to be upregulated in lymphoblastoid cells derived from lithium-responsive BD patients (Squassina et al., 2013), suggesting that one potential mechanism of lithium's action might involve the regulation of IGF-1 secretion, a known cell survival factor that prevents apoptosis (Fidaleo et al., 2017).

D. Factors Affecting Apoptotic Signaling

Apoptosis, the process of programmed cell death driven by signal transduction, has been a subject of extensive research. Seminal studies have revealed that lithium has several remarkable effects: 1) it elevates the expression of the B-cell lymphoma (Bcl-2) protein, a key regulator of programmed cell death; 2) it reduces the expression of proapoptotic proteins such as p53 and Bax; and 3) it hinders the release of cytochrome c from mitochondria induced by glutamate in cultured neurons (Chen and Chuang, 1999). In addition to its impact on neurons, chronic lithium administration also increases Bcl-2 protein levels in astrocytes, which are crucial for neuronal survival (Keshavarz et al., 2013). It is noteworthy that differences in Bcl-2 gene expression may serve as a distinguishing factor between lithium responders and nonresponders (Beech et al., 2014), suggesting that the effectiveness of lithium treatment might be linked to the preservation of neurons and their supporting cellular structures. Furthermore, valproate also exhibits antiapoptotic properties, hinting at a potential shared mechanism where mood stabilization coincides with the reduction of apoptotic pathways (Gupta et al., 2012).

When cells face harmful insults, lithium plays a protective role by preserving mitochondrial function, by reducing reactive oxygen species, thus preventing cell apoptosis (Hou et al., 2015).

Consistent with these findings, recent research affirms (confirms) that lithium protects the hippocampus from apoptosis by engaging neuroprotective and anti-inflammatory pathways (Liechti et al., 2014; Dwivedi and Zhang, 2015). Indeed, lithium decreased the expression of proapoptotic genes Bax, Bad, and caspase 3. Interestingly, a clinical study showed that BD patients who respond to lithium showed an increased ratio of anti- to proapoptotic genes in blood cells. In contrast, patients who do not respond to lithium had no significant effect (Lowthert et al., 2012). Thus, effects on pro- and antiapoptotic genes might underpin lithium action in clinical response to BD. There are several possibilities whereby lithium modulates the transcription of pro- and antiapoptotic genes. One could be that BDNF-induced activation of extracellular signal-regulated kinase (ERK) signaling may lead to increased expression of these genes. For example, the Bcl-2 gene contains binding sites for CREB, a transcription factor activated by ERK1/2.

Interestingly, lithium has earlier been shown to upregulate ERK expression in cultured cells and rats' frontal cortex and hippocampus (Chen and Manji, 2006). Furthermore, lithium also upregulates the expression of BAG-1, a gene that binds to and increases the activity of Bcl-2 (Zhou et al., 2005). Thus, the effect of lithium on Bcl-2 could be associated with increased expression of BAG-1 (Dwivedi and Zhang, 2015).

E. Intracellular Signaling Cascades

1. PI3K/Akt Pathway. As stated above, BDNF induction is an early and essential step in the neuroplasticity and neuroprotection activity of lithium as demonstrated using different animal models of traumatic brain injury (TBI) (Ciftci et al., 2020), cerebral ischemia (Fan et al., 2015; Ates et al., 2022), and many others (Dou et al., 2005; Nowicki et al., 2008). It has been suggested that neuroprotection may originate from activating the PI3K/Akt signal transduction pathway (Kilic et al., 2017). Additionally, the trophic influence of BDNF is intricately connected to the activation induced by lithium in cell survival pathways, specifically the PI3K/Akt and MEK/ERK (also known as the Ras-Raf-MEK-ERK) pathways (Chiu et al., 2013).

Akt, a serine/threonine kinase regulated by PI3K, experiences activation through phosphorylation at Thr308 and Ser473 residues (Jacinto et al., 2006). Notably, lithium has been shown to induce the phosphorylation of Akt at Ser473 (Tian et al., 2014; Fan et al., 2015). Early studies conducted with cultured rat cerebellar granule cells revealed that lithium rapidly counteracted Akt-glutamate-induced inactivation by stimulating PI3K, leading to increased phosphorylation of Akt at its Ser473 residue. This Akt activation triggers alterations

in Bcl-2-associated death promoter, CREB, members of the forkhead family, and procaspase-9, which are antiapoptotic targets (Chiu et al., 2013). Similarly, in cultured human neuroblastoma cells, lithium treatment demonstrated an inhibitory effect on caspase-3 activation induced by neurotoxins mimicking the neurochemical changes associated with PD. This inhibition occurred in a manner dependent on PI3K (King et al., 2001). More recently, Ates et al. (2022) reported that, in a mouse model of brain ischemia, the phosphorylation of Akt at Thr308 was significantly higher than that at the Ser473 residue following the administration of a therapeutic dose of 2 mmol/kg lithium. This finding suggests that the PI3K/Akt pathway plays a major role in lithium's neuroprotective activity.

2. MEK/ERK Pathway. Genetic studies of BD and molecular studies of lithium's mechanism have previously pointed to MEK/ERK pathways. Reduced phosphorylation of ERK1/2 has been observed in post mortem samples collected from the prefrontal cortex of patients with BD (Yuan et al., 2010) and in both the prefrontal cortex and hippocampus of individuals who died by suicide (Dwivedi et al., 2009). Preclinical studies showed that lithium might engage ERK to alter the expression of PER2 by activating the transcription factor *egr-1* (Kim et al., 2013). Furthermore, U0126, both a K252a and the MEK inhibitor, inhibits the antidepressant-like effects induced by BDNF (Shirayama et al., 2002), supporting the notion of TrkB's involvement in activating the MEK/ERK pathway. ERK, in turn, regulates several downstream effector systems, including the transcription factor nuclear factor κ -light-chain-enhancer of activated B cells (NF- κ B) and ribosomal S6 kinase (RSK). Additionally, ERK inhibits GSK3 β and activates CREB (Steelman et al., 2004). CREB functions as a shared downstream effector for both the PI3K/Akt and MEK/ERK signaling pathways. When it is activated through phosphorylation, it assumes a pivotal role in bolstering cell survival by upregulating the expression of cell-protective proteins, like BDNF and Bcl-2 (Finkbeiner, 2000). Interestingly, treatment with lithium enhances ERK phosphorylation; however, the lithium-induced enhancements in BrdU-positive cells and cognitive function were hindered by the administration of U0126 (Yan et al., 2007a). In addition, more recently ERK was identified as a regulator of lithium's effect on circadian rhythm amplitude in fibroblasts from BD patients and demonstrated that p-ERK1/2 is decreased in BD cells (McCarthy et al., 2013; 2016).

3. Wnt/ β -Catenin Pathway. Lithium serves multiple essential functions in maintaining the proper functioning of the nervous system, including its role in enhancing neurogenesis, synaptic plasticity, and cell survival (Chen et al., 2000b; Schloesser et al., 2008; Kim and Thayer, 2009). Neurogenesis, a critical process for hippocampal plasticity, continues throughout adulthood

in the mammalian brain. Furthermore, lithium contributes to learning and memory processes. Recent neuroimaging research underscores the significance of the hippocampus as a key target for the effects of lithium. Studies in mice and humans show an accumulation of lithium in the hippocampal regions of the brain after repeated oral administration (Zanni et al., 2017; Stout et al., 2020; Palmos et al., 2021). In addition, large meta-analyses from the ENIGMA neuroimaging consortium suggest that smaller hippocampal volumes are a common feature among psychiatric disorder patients (Hibar et al., 2016; van Erp et al., 2016; Logue et al., 2018). Nevertheless, individuals with bipolar disorder who are on long-term lithium treatment display larger hippocampal volumes compared with their nonmedicated counterparts within the BD patient group (Hajek et al., 2012). This indicates that lithium therapy could potentially mitigate the reductions in hippocampal volume typically observed in individuals with psychiatric disorders, either through the preservation of existing neurons or the stimulation of neurogenesis.

These data align with preclinical research indicating that mice treated with lithium experience increased neurogenesis, which is associated with the activation of Wnt signaling. This activation is evident through enhanced nuclear β -catenin staining in newly formed neurons (Fiorentini et al., 2010; Valvezan and Klein, 2012). The inhibition of GSK3 by Wnt canonical signaling allows the translocation of β -catenin to the nucleus and facilitates activation of β -catenin/TCF-LEF target genes critical for synapse plasticity and neurogenesis (Valvezan and Klein, 2012). Moreover, lithium's impact extends to suppressing astroglialogenesis through non-GSK3-mediated mechanisms. Consequently, lithium appears to enhance the neuronal differentiation of neural stem cells through a dual mechanism, promoting neurogenesis while curtailing astroglialogenesis (Zhu et al., 2011; Kerr et al., 2018). However, recent *in vitro* findings have suggested that high-dose lithium treatment at 2.25-mM levels can increase the generation of neuroblasts, neurons, and glial cells in human hippocampal progenitors. This treatment also influences the expression of genes responsible for regulating the molecular layer's volume in the dentate gyrus (Palmos et al., 2021). These findings support the idea that adult hippocampal neurogenesis and gliogenesis are mechanisms that could help explain the therapeutic effects of lithium.

4. Calcium/Calmodulin-Dependent Protein Kinase II/CREB Pathway and Calcium Channels. Lithium treatment not only exerts a neuroprotective action through Akt activation but also through calcium/calmodulin-dependent protein kinase II (CaMKII) activation and calcium mobilization, respectively, leaving an inhibition of apoptosis signaling (Kang et al., 2003). Indeed, activation of these kinases leaves a lithium-induced

neuroprotective function in a rat model of ischemia-induced brain injury (Sasaki et al., 2006).

CaMKII plays a critical role in neurotransmission, synaptic plasticity, learning, and memory. In post mortem brain samples from patients with BD, lower levels of CaMKII mRNA expression were reported in different laminae of Brodmann's area nine and area 46 compared with control subjects (Xing et al., 2002). These early observations suggested that decreased CaMKII expression/function in patients with BD seems to be associated with some of the affective and cognitive alterations reported in BD. Preclinical studies in rats confirmed that CAMKII-CREB signaling pathway activation in the hippocampus and prefrontal cortex are implicated in memory consolidation of inhibitory avoidance learning (Ghasemzadeh and Rezayof 2016; Amiri et al., 2020). Furthermore, Amiri et al. (2020) also reported that glutamate NMDA receptors are involved in the interactive effects of lithium and olanzapine on memory consolidation through the CAMKII-CREB signaling pathway.

Recent findings also focus on the role of calcium, calcium channels, and neuronal calcium sensor protein 1 (NCS-1) in the etiology of BD (D'Onofrio et al., 2017; Garcia-Rill et al., 2019). In the manic or mixed state, patients with BD display reduced auditory electroencephalogram synchronization in the β/γ band during a click train paradigm (O'Donnell et al., 2004). γ band oscillations are essential to information processing during states of arousal, such as sensory perception and motor behavior, and are thought to be involved in memory formation (Kann et al., 2014, Mably and Colgin, 2018). Therefore, a decrease in high-frequency γ band activity may underlie many of the symptoms of BD, such as sleep disturbances, emotional dysregulation, attention and memory deficits, and impairments in fine motor skills (Goldberg and Chengappa, 2009). Importantly, the reticular activating system, especially the pedunculopontine nucleus, generates γ oscillations via calcium channels, pointing to roles for the reticular activating system and calcium in the disease progression (D'Onofrio et al., 2017; Byrum et al., 2019). Human post mortem studies reported increased expression of NCS-1 in the brains of patients with BD and schizophrenia (Koh et al., 2003). Lithium appears to act by inhibiting the interaction between NCS-1 and inositol 1,4,5-triphosphate (IP3) receptor (Schlecker et al., 2006), preventing the action of excess NCS-1 and restoring intracellular pathways that mediate normal γ oscillations. Although low levels of NCS-1 allow high-threshold calcium channels to mediate intrinsic membrane oscillations, high levels of NCS-1 inhibit the oscillations. Therefore, optimal concentrations of lithium reduce the effects of NCS-1 overexpression by normalizing γ band activity.

F. Oxidative Stress Pathways and Mitochondrial Dysfunction

A growing body of evidence points to disrupted mitochondrial function in psychiatric conditions, including BD, as well as in neurodegenerative diseases that manifest psychiatric symptoms. In fact, various mitochondrial abnormalities have been documented in psychiatric disorders, encompassing reduced expression of peroxisome proliferator-activated receptor γ (PPAR γ), diminished mitochondrial respiration, imbalances in proinflammatory and apoptotic responses, and impaired mitochondrial motility (Pei and Wallace, 2018, Preston et al., 2018; Galts et al., 2019; Kolar et al., 2021; van Rensburg et al., 2022). BD is hypothesized as being a biphasic dysregulation of mitochondrial biogenesis, decreased in depression and increased in mania (Morris et al., 2017). Although exploring signaling pathways and mechanisms related to mitochondrial dysfunction exceeds the scope of this review, we will briefly report evidence indicating the involvement of oxidative stress pathways in several central nervous system disorders as well as their regulation by lithium.

Research involving individuals with bipolar disorder has indicated that lithium reduces levels of lipid peroxidation and enhances mitochondrial function, effectively countering the impacts of oxidative stress (Khairova et al., 2012; De Sousa et al., 2014, 2015). Using different animal models of cerebral ischemia or neurotoxicity induced by 3-nitro propionic acid or kainic acid, lithium was found to prevent neuronal sensitivity to oxidative damage (Rojo et al., 2008; Castro et al., 2009; Khan et al., 2015; Chen et al., 2016). The protective effects of lithium against oxidative damage are evident through several indicators, including reduced levels of lipid peroxidation, as measured by thiobarbituric acid reactive substances (TBARS) or 4-hydroxynonenal (4-HNE), decreased protein carbonylation, and a decrease in the production of reactive oxygen species (Shao et al., 2005; Rojo et al., 2008; Castro et al., 2009). Furthermore, lithium treatment has been shown to boost the expression of antioxidant enzymes such as catalase (Khan et al., 2015), heme-oxygenase-1 (HO-1) (Khan et al., 2015; Chen et al., 2016), and NAD(P)H quinone oxidoreductase-1 (NQO1) (Chen et al., 2016) as well as restoring levels of glutathione and glutathione-transferases (GstD1, GstD2), crucial mediators of neuronal defense against oxidative damage (Kerr et al., 2017).

Moreover, the inhibition of GSK3 mirrors many of these antioxidant properties of lithium. This has been shown in studies utilizing GSK3 antisense oligonucleotides, short-interfering RNAs, and specific GSK3 inhibitors (e.g., SB216763, TDZD-8) in rat models of cerebral ischemia and in the SAMP8 mouse model, which simulates aging-associated AD (Rojo et al., 2008; Chen et al., 2016). In this context, the transcription factor nuclear factor (erythroid-derived 2)-like 2 (Nrf2) has emerged

as a pivotal molecular mediator responsible for transmitting lithium's antioxidant effects following GSK3 activation. Nrf2 operates by upregulating the expression of a variety of genes containing antioxidant response elements, thus effectively mitigating oxidative damage (Kerr et al., 2018).

G. Protein Quality Control Mechanisms

1. Ubiquitin-Proteasome System and Autophagy. Protein homeostasis is the equilibrium between the synthesis and breakdown of proteins. For neurons, where the removal of impaired components cannot be accomplished via cellular division, qualitative adjustments to the proteome and the prompt removal of damaged and misfolded proteins are crucial processes (Douglas and Dillin, 2010; Balchin et al., 2016; Kerr et al., 2018). Intriguingly, lithium influences proteostasis by diminishing protein synthesis and augmenting protein degradation, thus regulating proteasomal activity and autophagy. These effects may hold promise for addressing a range of neurodegenerative diseases, such as AD, PD, and various forms of dementia. This potential benefit can be attributed to its ability to either enhance the clearance of abnormal protein aggregates, a common hallmark of these disorders, or maintain protein homeostasis for the proper function of neuronal cells. Furthermore, lithium promotes the breakdown of proteins prone to forming aggregates, including mutated huntingtin, phosphorylated τ , and α -synuclein (Motoi et al., 2014).

Although rapamycin is the most widely used pharmacological agent to induce autophagy through inhibition of the mTOR pathway, the mechanism by which lithium acts as an autophagy enhancer appears to be independent of the mTOR pathway. Several studies have identified the ability of lithium to deplete free inositol and subsequently lower IP₃ levels, through inhibition of IMPase and inositol transporters, as an mTOR-independent pathway to induce autophagy (Sarkar and Rubinsztein, 2006; Chiu et al., 2013). The lithium-caused "inositol depletion" has a positive feedback mechanism, in which the incremental effect of lithium is greater the higher the concentration of the IMP-IMPase complex (Harwood, 2005; Yu and Greenberg, 2016). This evidence led to the hypothesis that lithium may exert its therapeutic effect through inositol depletion, which mediates the autophagy effect. Lithium's ability to induce autophagy has mainly been showcased through animal models of neurodegenerative disorders characterized by the accumulation of misfolded proteins (Cuervo et al., 2004; Levine and Kroemer, 2008; Rubinsztein et al., 2012). More recent studies indicate the possible involvement of aberrant autophagy in schizophrenia as altered autophagy markers, e.g., beclin1 and microtubule-associated protein one light chain 3 (LC39), among others, have been identified in post mortem brain samples from patients with schizophrenia as well as in perinatal animal models of phencyclidine-

induced schizophrenia-like behavior (Yuan et al., 2015; Jevtic et al., 2016). Interestingly, although the search for studies linking autophagy to BD yields very few direct results, evidence points to mitochondrial dysfunction in BD because of impaired autophagy and, especially, to the role of mood stabilizers in its prevention (Toker and Agam 2015; Scaini et al., 2016; Bar-Yosef et al., 2019). Considering the robust therapeutic effects of lithium on mood disorders, autophagy may occupy a central place in its antimanic and antidepressant action. It is worth noting that the mood-stabilizing effects observed with certain drugs that induce autophagy, like valproate and rapamycin, are not unexpected. These medications are originally prescribed for different therapeutic purposes but have shown additional mood-stabilizing properties (Puglisi-Allegra et al., 2021).

2. Endoplasmic Reticulum Stress and Unfolded Protein Response Pathway. The endoplasmic reticulum (ER) serves as the main site for protein synthesis, folding, and trafficking within cells. Additionally, it functions as an intracellular calcium store and is extremely susceptible to disruptions in its internal environment, leading to ER stress. To ensure cell survival, the unfolded protein response (UPR) is activated as an adaptive reaction to ER stress. Both ER stress and abnormal UPR have significant implications in the development of various neuropsychiatric and neurodegenerative disorders, playing a central role in their pathogenesis. (Bengesser et al., 2016; Limanaqi et al., 2019). Numerous investigations have proposed that the UPR pathway might be involved in the pathophysiology of BD. Additionally, it has been suggested that mood stabilizers could potentially exert their therapeutic effects by triggering the activation of the UPR (Chen et al., 2000a; Kakiuchi et al., 2003; Shao et al., 2006; Kim et al., 2009; Pfaffenseller et al., 2014; Bengesser et al., 2016).

Evidence for altered UPR in BD comes from studies reporting an abnormal response to ER stress inducers. When stimulated with thapsigargin and tunicamycin, individuals with BD displayed either an unresponsive or reduced expression of UPR markers, including eIF2 α , GRP78 (Bip), GRP94, XBP1, and CHOP (Hayashi et al., 2009; Pfaffenseller et al., 2014). Remarkably, alterations in these markers appear to have predictive value for lithium responsiveness in BD (Breen et al., 2016). Lithium increases the expression of UPR chaperones (i.e., GRP78, GRP94, and calreticulin) in rats in both brain tissue and cultured cells (Shao et al., 2006). However, it is worth noting that some studies have reported that mood stabilizers have no significant impact on the UPR pathway. For instance, valproate led to increased GRP78 protein levels in HEK293 cells, but neither valproate nor lithium had a substantial effect GRP78 expression in Neuro-2a cells (Kakiuchi et al., 2003, 2009). Additionally, valproate and lithium did not induce changes in XBP1SH-SY5Y and lymphoblastoid

cells. (Kakiuchi et al., 2003). Despite these discrepancies, a substantial body of research in mammals strongly supports an induced activation of UPR by mood stabilizers. Several mechanisms have been proposed as potential contributors to potentially underlie the activation of the UPR by these mood stabilizers. These mechanisms include histone deacetylases inhibition, upregulation of the wolframin gene (WFS1), and myoinositol depletion (Shi et al., 2007; Kakiuchi et al., 2009; Jadhav et al., 2016), although these mechanisms have been described primarily for valproate (Sulliman et al., 2021).

H. Immunomodulatory Role of Lithium

New evidence indicates a correlation between an increased susceptibility to mood disorders and the inflammatory responses of the immune system, alongside alterations in the phenotype of macrophages triggered by the activation of microglia. Changes in the activation of microglia and the presence of inflammatory factors are also an early characteristic seen in individuals with dementia (Calsolaro and Edison, 2016; Sakrajda and Szczepankiewicz, 2021). There is also evidence revealing that mitochondrial dysfunction plays a crucial role in the development of neurodegenerative diseases, including AD, PD, Huntington disease (HD), amyotrophic lateral sclerosis (ALS), or multiple sclerosis, by increasing innate and adaptive immune responses that result in neuroinflammation (Garabadu et al., 2019; Zang et al., 2022). In addition, mitochondrial dysfunction and impaired energy metabolism are also involved in the pathophysiology of mood disorders (Kato, 2006; Cikankova et al., 2017; Allen et al., 2018; Culmsee et al., 2019). The mitochondrial hypothesis proposes a reciprocal relationship between changes in cell energy metabolism and inflammation. It suggests that disturbances in energy metabolism can activate the inflammasome, leading to elevated cytokine production and eventual apoptotic cell death. Conversely, inflammation can also impact the generation of energy within the cell (Ghosh et al., 2018; Kerr et al., 2018; Sakrajda and Szczepankiewicz, 2021; Tang et al., 2021). In this review, we will emphasize the pharmacological role of lithium as an immunomodulatory agent.

Previous research has indicated that lithium can reduce the levels of proinflammatory cytokines, both in peripheral tissues and within the central nervous system, and these changes have been linked to its efficacy (Boufidou et al., 2004; Beurel and Jope, 2014). Lithium's most well known mechanism of action is the inhibition of GSK3, which can impact various transcription factors, including NF- κ B. NF- κ B plays a critical role in the innate immune response and regulates the production of cytokines (Jope et al., 2007). The reduction in NF- κ B's transcriptional activity, induced by lithium's inhibition of GSK3 β , results in decreased production of proinflammatory

mediators such as interleukin (IL)-1 β , interferon- γ , IL-6, and MCP1, which are associated with M1 macrophages. Conversely, it increases the production of anti-inflammatory cytokines (Martin et al., 2005).

Another potential downstream target of GSK3 is a signal transducer and activator of the transcription (STAT) family. There are seven members of the STAT protein family in mammals. Among them, STAT3 was discovered as a component of the IL-6-activated acute phase response factor (APRF) complex, which has a crucial role in stimulating the expression of innate immune mediators (Hillmer et al., 2016). Furthermore, GSK3 phosphorylates and activates STAT3 by facilitating its interaction with the proinflammatory interferon- γ receptor as demonstrated in primary astrocytes from mice. Treatments with lithium or GSK3 inhibitor TDZD-8 treatment blocks these effects (Beurel and Jope, 2009; Rowse et al., 2012).

In addition, molecular mediators of the anti-inflammatory effects of lithium also correlate with Toll-like receptor 4 (TLR4) pathways (Kerr et al., 2018). TLR4 serves as a pattern-recognition receptor responsible for detecting specific pathogen-associated molecular patterns, such as lipopolysaccharide, along with cytokines. After binding to its ligand, TLR4 recruits signaling adaptors and initiates a series of signaling cascades that result in the activation of NF- κ B and the release of inflammatory cytokines (Lien et al., 2000; Cheong et al., 2011). The anti-inflammatory effects of lithium via suppression of microglial activation and attenuation of overexpression of proinflammatory cytokines and chemokines are thought to be dependent on TLR4 signaling. Indeed, lithium inhibited lipopolysaccharide-induced TLR4 expression and microglial activation through the PI3K/Akt/FoxO1 signaling pathway (Dong et al., 2014). Furthermore, changes in the levels of TLR4 expression and its associated transcription factor NF- κ B were found to be associated with lithium's ability to alleviate memory deficits in elderly rats. This improvement in memory was connected to reductions in the levels of TNF- α and IL-1 β in the hippocampus (Lu et al., 2015; Cheng et al., 2016). Taken together, these data suggest that lithium's anti-inflammatory and neuroprotective effects may be mediated independently of GSK3 inhibition through modulation of TLR4, NF- κ B, and STAT3 signaling.

IV. Ketamine, Lithium, and the Targeting of Homeostatic Synaptic Plasticity

Recent studies indicate that ketamine and lithium target the same synaptic process, i.e., elicit functional synaptic plasticity (Kavalali and Monteggia, 2020; Price et al., 2021), albeit their targets are widely divergent, and their mechanisms are different. Therefore, combined lithium and ketamine treatment may enhance antidepressant responses by promoting molecular signaling cascades and bioenergetic pathways essential to

enable synaptic processes. Over the last 10 years, clinical research has shown that administering a low dose of ketamine intravenously leads to a swift and effective antidepressant response in individuals with depression, including those with treatment-resistant depression and bipolar depression (Berman et al., 2000; Zarate et al., 2006b; Price et al., 2009; Daly et al., 2018; Wilkowska et al., 2020). Ketamine is recognized as a noncompetitive antagonist of the glutamatergic N-methyl-D-aspartate receptor (NMDAR), and several initial targets for its actions have been proposed in the literature. These targets include NMDARs on GABA interneurons (Homayoun and Moghaddam 2007; Quirk et al., 2009) and NMDAR and AMPAR on pyramidal neurons (Zanos et al., 2016; Artigas et al., 2018). Similar to other rapid-acting antidepressant treatments (Duman et al., 2016; Jiménez-Sánchez et al., 2016), ketamine's mechanism of action involves the activation of AMPARs. This effect may result from the blockade of NMDARs in specific subsets of GABA neurons or direct activation of AMPARs. Studies utilizing $[^1\text{H}]$ -magnetic resonance spectroscopy have revealed that ketamine increases the levels of glutamine, which serves as a marker for glutamatergic transmission, in the anterior cingulate cortex of healthy individuals (Rowland et al., 2005). Similarly, research employing $[^{13}\text{C}]$ -NMR in rats has shown that ketamine increases cortical labeling of glutamate, glutamine, and GABA (Chowdhury et al., 2012). These findings align with previous observations of increased glutamate efflux using microdialysis procedures (Adams and Moghaddam, 2001). Nevertheless, the antidepressant effects of ketamine can be blocked by opioid receptor antagonists (Williams et al., 2018). These observations indicate that ketamine, at least in part, enhances presynaptic glutamatergic neurotransmission, leading to rapid upregulation of AMPAR and BDNF/TrkB activation to promote neurotrophic signaling through mTOR activation (Li et al., 2010) and GSK3 β inhibition (Beurel et al., 2011). These molecular cascades, in turn, have been shown to functionally promote the development of new synaptic connections to enhance connectivity between mood-related brain regions (Duman and Aghajanian, 2012; Costemale-Lacoste et al., 2016; Gerhard et al., 2016; Zarate and Machado-Vieira, 2016; Fullana et al., 2022).

Lithium activates neurotrophic and neuroprotective cellular cascades (Quiroz et al., 2004, 2010; Sinha et al., 2005; Dwivedi and Zhang, 2015; Costemale-Lacoste et al., 2016), including the stimulation of neurotrophic molecular pathways (i.e., BDNF/TrkB and mTOR activation, GSK3 inhibition) (Machado-Vieira et al., 2009; Gideons et al., 2017), direct modulation of bioenergetic factors (i.e., increased IGF expression) (Fidaleo et al., 2017; Price et al., 2021), and protection of mitochondrial health, cellular energy metabolism, and antioxidant defense (Rojo et al., 2008; Castro et al., 2009; Kerr et al.,

2018). Certainly, some of the most consistently observed findings in this context involve the inhibition of GSK3, the upregulation of neurotrophins, and shifts in AMPAR expression (Hashimoto et al., 2002; Pisanu et al., 2016; Kavalali and Monteggia, 2020; Price et al., 2021). Recent investigations into the synaptic mechanisms influenced by lithium have unveiled a significant reduction in AMPAR-mediated miniature excitatory postsynaptic current amplitudes. This reduction is contingent on BDNF and its TrkB receptor (Gideons et al., 2017). Such an effect on glutamatergic neurotransmission may play a role in counterbalancing the heightened glutamatergic signaling observed in individuals with BD during manic episodes (Ongür et al., 2008; Lan et al., 2009). Furthermore, these findings align with additional evidence gathered from post mortem brain tissue of individuals with BD (Hashimoto et al., 2007; Eastwood and Harrison, 2010). Electrophysiological recordings in human neurons derived from induced pluripotent stem cells of patients with BD have also indicated molecular and functional alterations associated with increased glutamatergic neurotransmission (Mertens et al., 2015). Notably, the decrease in cell surface AMPAR expression is contingent on BDNF/TrkB signaling (Gideons et al., 2017). Consequently, although lithium elevates BDNF expression and diminishes AMPAR function, ketamine also increases BDNF levels, leading to enhanced AMPAR responses. Further research is essential to unravel the intricate mechanisms through which BDNF/TrkB signaling, influenced by either ketamine or lithium, can evoke such diverse effects at both synaptic and behavioral levels.

Downstream of these mechanisms, both lithium and ketamine initiate neurotrophic cascades through activation of MEK/ERK and CREB pathways, which provide bioenergetic stimuli for neuronal and synaptic plasticity, and play a critical role in antidepressant responses (Kim et al., 2013; McCarthy et al., 2016; Réus et al., 2016). Consequently, lithium is a promising candidate for adjunctive treatment to ketamine and has shown potential as a boosting agent for other antidepressant approaches for treatment-resistant depression and bipolar depression (Nelson et al., 2014; Costi et al., 2019; Caldiroli et al., 2021). For example, in a rodent model of treatment-resistant depression, augmentation of imipramine with lithium was shown to promote central and peripheral insulin signaling, which directly correlated with the antidepressant behavioral response (Walker et al., 2019). In addition, lithium has been shown to potentiate the synaptogenic and antidepressant effects of subthreshold doses of ketamine in naive rats (Liu et al., 2013). Similarly, lithium was found to enhance the antidepressant response to ketamine in antidepressant-unresponsive animals, along with peripheral insulin efflux and region-specific prefrontal cortex insulin signaling (Price et al., 2021). However, Xu

et al. (2015a) reported that therapeutic doses of lithium (0.79 ± 0.15 mEq/L in serum) did not correlate with an improvement in antidepressant efficacy of ketamine at a dose of 0.5 mg/kg in treatment-resistant bipolar depression. Some considerations should be taken into account for a plausible explanation of the differences obtained between preclinical and clinical studies on the lithium effects as an enhancer of the antidepressant ketamine action (Liu et al., 2013; Xu et al., 2015a). These include 1) the difference in the experimental design of the studies; 2) the small number of patients included ($n = 23$ subjects), not sufficient for statistical power; 3) the use of subtherapeutic doses of lithium and ketamine in the animal model, whereas patients received stable therapeutic levels of lithium for 4 weeks prior to ketamine infusion; and 4) treatment-refractory patients versus an untreated rat model as well as other variables directly related to differential metabolism between humans and rodents. In any case, further studies are needed to determine the appropriate timing of administration of lithium or selective GSK-3 inhibitors to enhance the synaptic and antidepressant effects of ketamine. Based on the broad pharmacology of ketamine and lithium, these data support that essential synaptic plasticity may provide new insights and targets for advancing the treatment of mood disorders.

V. Biology of Lithium's Response

Clinical response to lithium when used as a mood-stabilizer agent varies considerably, with half of the patients showing an incomplete response. Family studies showed a pattern of heritability of response to lithium among generations (Grof et al., 2002). Both heterogeneity and familiar transmission of the response could be explained on genetic bases. Candidate-gene studies were able to identify a large number of genes coding for GSK3 β , BDNF, and the serotonin transporter associated with lithium response (Pisanu et al., 2018). However, the mild effect of these variants suggested the hypothesis of a polygenic nature of lithium response. Genome-wide association studies (GWAS) are ideal to study complex traits or diseases since they test the association between millions of common genetic variants distributed across the human genome with a specific phenotype on large populations (Tam et al., 2019). Results of GWAS studies on lithium response are, to date, contrasting, with several studies failing to find genome-wide associations replicating previous results (Perlis et al., 2009, Squassina et al., 2011). A study that used a formal definition of clinical response to lithium (i.e., using the Alda Scale) (Manchia et al., 2013) identifies two significant single nucleotide polymorphisms (SNPs) located in the glutamate-decarboxylase-like protein 1 (GADL1) associated with lithium response (Chen et al., 2014). These results might

support the importance of the glutamatergic system in lithium response (McCarthy et al., 2010).

Despite GWAS providing insights into the genetics of lithium response, they face several limitations. These include small sample sizes, challenges in replicating results across diverse ancestries or populations, and the use of heterogeneous definitions for clinical response to lithium. To overcome these limitations, the ConLiGen collaborative consortium was established in 2008 to facilitate high-quality, well powered analysis of lithium treatment response data (Schulze et al., 2010).

In a GWAS from the ConLiGen consortium on 2563 patients with BD, a single locus for four linked SNPs on chromosome 21 was associated with lithium response (Hou et al., 2016).

Individuals carrying these alleles linked to treatment response exhibited a reduced relapse rate in an independent prospective study involving 73 patients receiving lithium monotherapy. The identified region encompasses two long noncoding RNA genes (AL157359.3 and AL157359.4), implying their potential role as regulators of gene expression in the central nervous system (Hou et al., 2016).

GWAS, despite their limitations, can nowadays be used to calculate the polygenic risk score (PRS), which is a numerical score that quantifies an individual's genetic risk for a particular trait (as for example lithium response) or disease based on the cumulative effect of multiple genetic variants, typically SNPs scattered across the genome. Although GWAS on lithium response failed to generate good estimates to calculate the lithium response-PRS due to lack of statistical powers, PRSs of other phenotypes have been used to predict lithium response in BD. Indeed, higher schizophrenia and major depression PRSs were associated with poorer response to lithium, whereas BD-PRS showed no such association (Schubert et al., 2021). In a multiethnic study, individuals with higher PRS for major depressive disorder were less likely to respond to lithium treatment compared with those with lower scores in the multiethnic sample and in the European sample, though no significant association was observed in the Asian sample (Amare et al., 2021). In another sample, a higher PRS for attention-deficit/hyperactivity disorder or major depression was associated with a poorer response to lithium (Coombes et al., 2021). As for GWAS, the effect size estimate for PRS is modest as well as the generalizability of the results. Nevertheless, PRS with clinical variables and using machine-learning models might significantly improve the prediction of lithium response (Cearns et al., 2022).

In a flow-cytometric study, the expression levels of 28 intracellular proteins in CD4⁺ lymphocytes and monocytes were analyzed before and after 16 weeks of lithium treatment in patients with BD, divided according to lithium response. Results showed that lithium induced divergent changes in protein expression depending

on an individual's response to treatment (Gao et al., 2023).

Furthermore, a network-based integrative analysis of transcriptomic and genomic data revealed 41 differentially expressed genes in lithium responders versus non-responders, and post-GWAS gene prioritization identified 1119 candidate genes. Functional enrichment highlighted focal adhesion and the extracellular matrix (ECM) as the most significant functions, emphasizing the importance of dysregulation in these pathways in understanding lithium response and underlying BD mechanisms (Niemsiri et al., 2023).

Induced pluripotent stem cells (iPSCs) have emerged as a valuable tool in BD research in disease modeling, drug screening, and personalized medicine. iPSCs are somatic adult cells that have been reprogrammed to exhibit pluripotent characteristics, meaning they can differentiate into any cell type in the human body, including neurons. In a recent study, an iPSC model for BD was created, identifying mitochondrial abnormalities and hyperactive action-potential firing in young neurons derived from patients with BD. The hyperexcitability phenotype was selectively reversed by lithium treatment in neurons from responsive patients, suggesting that iPSC models may aid in the development of targeted therapies for BD (Mertens et al., 2015). Indeed, circadian rhythms in neuronal precursor cells (NPCs) and reprogrammed glutamatergic neurons were disrupted to a greater extent in samples obtained from lithium nonresponders as compared with lithium responders (Mishra et al., 2021). Furthermore, in iPSC models, lithium increases mitochondrial respiration capacity only in lithium responders, suggesting involvement of mitochondrial functions in the mechanisms of mood stabilizers (Osete et al., 2021). iPSC-derived brain organoids have also been studied to model BD. One study explored the effects of long-term lithium treatment on iPSC-derived human cortical spheroids from healthy controls and patients with BD (Osete et al., 2023). BD human cortical spheroids displayed altered neuronal characteristics compared with controls, and lithium treatment exerted opposite effects on neuronal excitability between BD and controls. Also, 132 lithium-associated differentially expressed genes related to sodium ion homeostasis and kidney-related pathways were identified in the same study, highlighting the potential of iPSC-derived three-dimensional brain models for precision medicine in psychiatry (Osete et al., 2023). Although these studies are intriguing, their connection with the individual genomic load of each patient concerning lithium response has yet to be established.

VI. Lithium-Modified microRNA Pathways

MicroRNAs (miRNAs) have arisen as regulators of gene expression post-transcriptionally, albeit they are not classified as part of the epigenetic machinery. Their

involvement extends across nearly all biologic processes, encompassing cell proliferation, development, differentiation, and programmed cell death. The identification of over 1500 miRNA genes highlights their pivotal role, with each miRNA having the potential to target multiple mRNAs. Highlighted by their multifaceted role, miRNAs hold considerable importance in shaping cellular states and outcomes (Lin and Gregory, 2015) given their ability to either inhibit the translation of target mRNA or expedite its degradation. Moreover, they can serve as enhancers of translation or even impact transcription by binding to gene promoters. Considering the intricate nature of the nervous system at both the cellular and transcriptional levels, it is not surprising that approximately 75% of annotated miRNAs find expression within the brain (Kosik, 2006, Artigas et al., 2018; Bortolozzi et al., 2021). Intriguingly, miRNAs can be released from the brain and enter circulatory bio-fluids, where they remain remarkably stable (Cheng et al., 2014; Żurawek and Turecki, 2021; Clausen et al., 2022). Alterations in the miRNA levels have been reported in brain tissue as well as in blood from patients with mood disorders, including BD (Forstner et al., 2015; Maffioletti et al., 2016; Fries et al., 2018; Clausen et al., 2022). Interestingly, several studies have shown that lithium modifies the expression of miRNAs and their targeted mRNA (Chen et al., 2009; Hunsberger et al., 2015; Reinbold et al., 2018; Pisanu et al., 2019; Marie-Claire et al., 2021), suggesting that they could play a role in modulating lithium's clinical efficacy.

Here, we summarize translational studies showing the involvement of miRNAs in lithium's actions (Table 1). Previous studies have identified several miRNAs and their predicted mRNA effectors in the rat hippocampus as targets for the action of mood stabilizers (Zhou et al., 2009). Some of these miRNAs, such as miR-221 and miR-34a, have been shown to be influenced by lithium treatment in lymphoblastoid cell lines derived from patients with BD (Chen et al., 2009). Although certain miRNAs, like miRNA-134, have been linked to treatment response in bipolar mania, (Rong et al., 2011), the majority of available data suggests that lithium's impact on miRNA levels is largely independent of its clinical efficacy. A recent study compared miRNA and targeted mRNA expression profiling of lymphoblastoid cell lines before and after *in vitro* lithium treatment to identify networks of miRNAs and their targets involved in lithium response (Hunsberger et al., 2015). The lymphoblastoid cell lines used in the study were obtained from both lithium-responsive and nonresponsive BD patients. The results indicated that *in vitro* lithium treatment led to the downregulation of the Let-7 family of miRNAs in both groups. Furthermore, a genome-wide analysis of miRNAs in 2563 patients, categorized by their response to lithium, identified 15 miRNAs significantly associated

TABLE 1
Studies reporting the effects of lithium on miRNA expression

miRNAs	Samples	Method	Target Genes	Lithium Effects	Reference
miR-221, miR-152, miR-15a, miR-494, miR-155, miR-181c, miR-34a, miR-605, miR-17-3p, miR-148a, miR-200C, miR-181b, miR-513	Lymphoblastoid cell lines; BD (n = 20); LiCl treatment at 1 mM for 4 and 16 days	RT-qPCR	miRNA-targets were predicted by miRanda or TargetScan. Five genes (AP2A1, AP2S1, CD2AP, EIF1, and VCL) were significantly enriched and linked to biologic processes, i.e., complex macromolecular assembly, protein complex assembly, and cellular component assembly	Day 4: Increased miR-221, miR-152, miR-15a, and miR-155 and decreased miR-494 levels Day 16: Lithium increased miR-221, miR-152, miR-155 and miR-34a levels	Chen et al., 2009
Let-7b, let-7c, miR-105, miR-128a, miR-24, miR-30c, miR-34a, miR-221, miR-144, miR-136, miR-134	Kyoto Wistar rats; hippocampus samples; Li ₂ CO ₃ 1.2 g/kg for 1 week Human plasma, drug-free BD patients (n = 21)	Microarray and RT-qPCR	Predicted miRNA-targets: PTEN, axonal guidance, ERK, Wnt/ β -catenin, and β -adrenergic signaling pathways Not reported	Reduced levels of let-7b, let-7c, miR-128a, miR-24a, miR-30c, miR-34a, and miR-221, and increased miR-144 levels Increased miR-134 after 4 weeks of combined treatment with antipsychotics and mood stabilizers (lithium and valproate)	Zhou et al., 2009 Rong et al., 2011
miR-34a, miR-147, miR-182, miR-222, miR-495, and miR-690	Rat cerebellar granule cells; LiCl 3 mM for 6 days	Affymetrix GeneChip, RT-qPCR	Predicted miRNA-targets: TGF- β signaling, KEGG pathway, and other pathways including axonal guidance, focal adhesion, actin cytoskeletal regulation, and long-term potentiation	Increased miR-182, miR-147, and miR-222 following the combination treatment with lithium + valproate. miR-34a and miR-495 were both shown to be downregulated following combination treatment.	Hunsberger et al., 2013
Let-7 miRNA	In vitro study comparing vehicle versus chronic lithium treatment in patient-derived lymphoblastoid cells from either responders or non-responders (n = 8)	GRANITE	Predicted miRNA-targets: Let-7 miRNA family has been implicated in neurodegeneration, cell survival, and synaptic development	Let-7 family is consistently downregulated by lithium in both groups, where this miRNA family has been implicated in neurodegeneration, cell survival, and synaptic development	Hunsberger et al., 2015
miR-124	Mouse model of focal cerebral ischemia; LiCl 1 mg/kg bolus then 2 mg/kg/day for 7 day BD (n = 2,563)	RT-qPCR	miR-124 target: RE1-silencing transcription factor (REST, also known as NRSF)	Lithium increased miR-124 expression	Doepfner et al., 2017
1,692 miRNAs were tested		ConLiGen GWAS dataset	Not reported	Fifteen miRNAs associated with lithium response, among them miR-499a showed a robust association with lithium response	Reinbold et al., 2018
miR-320a, miR-155-3p, and their target genes were validated	Lymphoblastoid cell lines from BD patients ER (n = 12) and NR (n = 12) to lithium	Microarray and RT-qPCR	Validated miRNA-targets: calpain small subunit 1 (CAPNS1), regulator of G protein signaling 16 (RGS16), transcription factor SP4 (SP4) disorders (miR-320a and SP4)	Thirty-one miRNAs were differentially expressed in ER versus NR and inversely correlated with 418 genes differentially expressed between the two groups.	Pisanu et al., 2019

Squassina et al., 2020

(continued)

TABLE 1—Continued

miRNAs	Samples	Method	Target Genes	Lithium Effects	Reference
miR-4286, miR-337-3p, miR-186-5p, miR-423-5p	LCLs from patients with BD who died by suicide (SC, n = 7) and with a low risk of suicide (LR, n = 11). Therapeutic concentrations (1 mM) of LiCl or drug-free were evaluated.	nCounter miRNA expression Assay (Nanoscripting and RT-qPCR)	miR-4286 targets part of the insulin resistance pathway	Two miRNAs at baseline (miR-4286, miR-337-3p) and three in-cell lines treated with LiCl (miR-4286, miR-186-5p, miR-423-5p) were differentially expressed between SC and LR. miR-4286 was increased in SC compared with LR at baseline, whereas miR-186-5p was decreased in lithium-treated LCLs from SC compared with HC. Mir-4286 was also increased in the lithium-treated LCLs	

ER, excellent responder to lithium; GRANITE, Genetic Regulatory Analysis of Networks Investigational Tool Environment; KEGG, Kyoto Encyclopedia of Genes and Genomes; LCL, lymphoblastoid cell line; LR, low risk of suicide; NR, non-responder to lithium; RT-qPCR, quantitative reverse-transcription polymerase chain reaction; SC, suicidal.

with two lithium response phenotypes (Reinbold et al., 2018).

Furthermore, Pisanu et al. (2019) reported differential expression levels of 31 miRNAs in lymphoblastoid cell lines from individuals who exhibited excellent responses to lithium compared with nonresponders. Notably, changes in miRNA levels showed an inverse correlation with 418 differentially expressed genes in the two groups. Overall, these data provided new insights into the molecular processes involved in lithium effects that may help us fill the gap between molecular functions and the clinical efficacy of mood stabilizers.

VII. Repurposing Lithium for Brain Disorders Beyond Bipolar Disorder

In addition to effectively treating BD, lithium is currently under active investigation for a broad array of neuropsychiatric (i.e., treatment-resistant depression, suicidal behavior, post-traumatic stress disorder, schizophrenia, and autism spectrum disorder) and neurologic and neurodegenerative (i.e., PD, HD, AD and frontotemporal dementia, ALS, TBI, and stroke) disorders as well as gastrointestinal disease, cardiovascular disease, and neoplasia, among other conditions. In addition, as of July 2022, the US National Institutes of Health lists 191 planned, recruiting, or active clinical trials for lithium effects on several disorders (<http://www.clinicaltrials.gov>). In this section, we will present a summary of promising translational research and provide a concise overview of the current knowledge regarding the mechanism responsible for lithium-induced neuroplasticity and neuroprotection in neurologic and neurodegenerative disorders.

A. Parkinson Disease

Several studies have provided evidence of lithium's neuroprotective properties in cellular and animal models of PD (Kim et al., 2011; Lieu et al., 2014; Hou et al., 2015; Lazzara and Kim, 2015; Guttuso et al., 2019; Zhao et al., 2019; Vallée et al., 2021). Accumulation and aggregation of the α -synuclein protein, one of the main histopathological features of PD, may lead to dysfunctional autophagy and lysosomal processes (Cuervo et al., 2004). Lithium treatment reduces α -synuclein aggregation by targeting autophagy through the Akt/mTOR pathway (Motoi et al., 2014). Furthermore, mitochondrial complex I inhibitors like 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and rotenone are commonly used neurotoxins to induce PD-like symptoms in animal models (Cannon et al., 2009). Notably, lithium treatment has been found to alleviate rotenone-induced toxicity in human neuroblastoma SH-SY5Y cells. This protective effect is characterized by reduced nuclear fragmentation and apoptosis, accompanied by an increase in autophagy markers (Xiong et al., 2011). Furthermore, in an MPTP mouse model treated with lithium,

researchers observed a decline in mitochondrial membrane potential, decreased generation of reactive oxygen species, and an enhanced presence of lysosomes and autophagy vacuolar organelles (Li et al., 2013). Likewise, lithium administration protects against oxidative stress in a transgenic mouse model with overexpression of mutant A53T α -synuclein (Kim et al., 2011). Other preclinical studies reported that transplantation of stem cells preincubated with lithium in rodents with PD improves cognitive functions and motor coordination in these animals through the regulation of the Wnt/ β -catenin signaling pathway (Qi et al., 2017). Currently, an active phase 1 clinical trial (clinicaltrials.gov identifier: NCT04273932) is investigating lithium therapy as a potential disease-modifying therapy in PD (McFarthing et al., 2022).

B. Huntington Disease

Previous preclinical studies reported that lithium treatment induces considerable protection against neurodegeneration in an HD-like fly model by inhibiting IMPase and reducing inositol and IP₃ levels (Sarkar et al., 2008). In addition, other studies showed that 1–10 mM lithium enhances the autophagy of transfected mutant huntingtin in COS-7, SKNSH, PC12, and mouse embryonic fibroblast cells. Lithium has mixed effects on autophagy, improving it by downregulating GSK-3 β , inositol species, and cytoplasmic transcription factor p53 or, at higher lithium doses, reducing autophagy by activating mTOR through GSK-3 β inhibition (Chiu et al., 2011; Lauterbach, 2013). In addition, early studies on lithium reported its neuroprotective effects against apoptotic processes at clinically relevant concentrations using various striatal cell culture models of HD, i.e., striatal medium spiny neurons from YAC128 transgenic mice, striatal cells exposed to mutant huntingtin, or excitotoxic quinoline (Senatorov et al., 2004). Similarly, lithium exhibits neuroprotective properties in the quinoline injection model, not solely by inhibiting apoptosis but also by promoting the proliferation of neuronal and astroglial progenitors within the striatum or facilitating their migration from the subventricular zone (Senatorov et al., 2004). Low-dose lithium (20–40 μ g/kg per day per rectal mucosal absorption) reversed BDNF deficits in the YAC128 HD transgenic mouse (Pouladi et al., 2012). Decades ago, lithium's clinical application in patients with HD was investigated before its neuroprotective properties were recognized. Remarkably, lithium demonstrated a significant reduction in chorea and remarkable improvement in voluntary movements and motor function in patients with HD. Individuals in the initial phases of the disease appeared to derive greater benefit from lithium treatment, experiencing advantageous mood and temperament stabilization (Chiu et al., 2013). Conversely, other clinical studies showed that lithium did not yield any favorable effects in individuals with HD (Chiu et al., 2013).

Currently, there are no ongoing clinical trials for lithium and HD. The latest one (clinicaltrials.gov identifier: NCT00095355) was designed to examine whether lithium, given alone or with divalproex, increases BDNF levels in the cerebrospinal fluid of HD patients.

C. Alzheimer Disease

Lithium has been proposed as a potential therapy for dementia as positive effects have been described in cellular and animal models of dementia (Tsaltas et al., 2009; Forlenza et al., 2012; Hampel et al., 2019). There is evidence for its neuroprotective effects from experimental research and clinical studies using brain imaging (Kessing et al., 2010; Puglisi-Allegra et al., 2021; Chen et al., 2022b). Two meta-analyses (Matsunaga et al., 2015; Velosa et al., 2020) and a subsequent randomized controlled trial (Forlenza et al., 2019) have suggested that lithium has beneficial effects on cognition in mild cognitive impairment and AD. Lithium has the capacity to intervene at various points in the biochemical processes associated with the onset and progression of AD. This includes enhancing autophagy, exerting antiapoptotic effects, and initiating neurotrophic cascades. For example, several preclinical studies showed that therapeutic doses of lithium leave a decrease in τ protein hyperphosphorylation through inhibition of GSK3 β , resulting in a reduction of cognitive impairment in rodents (Phiel et al., 2003; Nakashima et al., 2005; Engel et al., 2006; Sudduth et al., 2012).

Accumulation of autophagy vacuoles has been demonstrated in post mortem brain tissue from AD patients, possibly due to altered autophagy vacuole clearance, but it may also reflect a flawed process of downstream lysosomal degradation (Boland et al., 2008; Barnett and Brewer, 2011). Once more, it is worth noting that lithium-induced autophagy might act in opposition to the anticipated autophagy suppression observed in AD. This suppression is attributed to the gradual rise in mTOR activity throughout the progression of the disease (Tramutola et al., 2015; Damri et al., 2020).

In addition, lithium favors synthesizing and releasing neurotrophic factors such as BDNF, whose increased availability promotes cell survival, stimulates hippocampal neurogenesis, and increases synaptic plasticity (Kerr et al., 2018; Forlenza et al., 2019). Indeed, accumulation of β -amyloid ($A\beta$) in the brain is associated with memory decline in healthy individuals as a prelude to AD. BDNF polymorphisms have been identified as potential moderators of $A\beta$ -related cognitive decline in preclinical AD (Lim et al., 2015). Moreover, BDNF has been shown to reduce $A\beta$ production within the brain (Nigam et al., 2017). However, BDNF therapeutic potential is hindered by its short half-life and its inability to penetrate the blood-brain barrier (Wurzelmann et al., 2017). Lithium can effectively activate the molecular pathway that increases BDNF synthesis. Recently, a new microdose

formulation of lithium, NP03, has been reported to be effective in amyloid pathology after the onset of A β plaques by increasing BDNF levels and reducing markers of neuroinflammation and cellular oxidative stress (Wilson et al., 2020; Kok et al., 2022). Additionally, although the precise molecular mechanisms responsible for lithium's anti-inflammatory effects in dementia models remain unclear, there is correlational evidence implicating the involvement of GSK3, STAT, and NF κ B pathways in playing a causative role (Jope et al., 2017; Kerr et al., 2018). Lastly, there is epidemiology evidence that levels of lithium in drinking water are associated with the risk for dementia (McGrath and Berk, 2017). Taken together, these preclinical data support that lithium has a crucial role in AD, encouraging clinical studies in patients to evaluate the efficacy of lithium in contrasting A β and τ pathology (Velosa et al., 2020). Several clinical trials are currently in progress focusing on the effect of lithium as a treatment to prevent impairment of cognition in elders (clinicaltrials.gov identifier: NCT03185208) as well as in the treatment of psychosis and agitation in AD (clinicaltrials.gov identifier: NCT02129348).

D. Amyotrophic Lateral Sclerosis

The pathogenesis of ALS involves interconnected processes, including altered proteostasis, ER stress, abnormal UPR signaling, mitochondrial dysfunction, and impaired autophagy. Interestingly, lithium treatment has demonstrated efficacy in ALS patients who possess genetic variations in the UNC13 presynaptic protein. These genetic variations are linked not only to ALS spectrum disorders but also to psychiatric conditions (Lipstein et al., 2017; Nakamura et al., 2018; Limanaqi et al., 2019). Lithium's neuroprotective and neurotrophic effects on motor function are achieved by targeting processes associated with UPR signaling, excitotoxicity, and autophagy dysfunction, whether at synapses or in cell bodies.

Markers of ER stress and UPR are increased in the blood and the spinal cord in both ALS patients and ALS-like mouse models. Notably, the activation of XBP1 represents an early pathologic event in motor neuron disease (Ilieva et al., 2007; Hetz et al., 2009; Ito et al., 2009; Montibeller and de Bellerocche, 2018; Vats et al., 2018). Studies conducted *in vitro* suggest that lithium can alleviate ER stress by inhibiting GSK3 β (Song et al., 2002; Takadera et al., 2007) and modulate gene transcription via the PKC-GSK3 β (Chen et al., 2000a; Hiroi et al., 2005). Lithium also has the potential to mitigate ER stress and aberrant UPR signaling by stimulating autophagy. In fact, the administration of lithium resulted in reduced levels of ER stress-related proteins, including GRP78, ATF-6, and CHOP, while simultaneously enhancing the autophagy process to safeguard motor neurons in the spinal cord (He et al., 2017; Tong et al., 2018). Similarly, lithium provides neuroprotective

effects, postpones the onset and duration of the disease, and extends the lifespan in G93A SOD-1 mice—mutations in copper-zinc superoxide dismutase 1 (SOD1) are a known genetic cause of ALS, and the SOD1 G93A mouse has been used extensively to investigate molecular mechanisms in ALS (Kreilaus et al., 2020)—by triggering autophagy, promoting the generation of mitochondria, and inhibiting reactive astrogliosis (Fornai et al., 2008). In recent studies, it has been discovered that lithium exerts neuroprotective effects by suppressing the upregulation of Notch signaling and postsynaptic protein Homer1b/c in the spinal cord of G93A SOD-1 mice. This mechanism leads to an increase in the Bcl-2/Bax ratio, contributing to the neuroprotective properties of lithium in this context (Wang et al., 2015; Jiang et al., 2016).

Moreover, a clinical study showed significant benefits in ALS patients who received riluzole plus lithium for 15 months compared with those who received riluzole alone. Lithium delayed disease progression in ALS patients as assessed by quantitative measures of muscle strength and preservation of lung function (Fornai et al., 2008). Similarly, the combined administration of lithium and valproate significantly extended the survival of ALS patients and provided neuroprotection by elevating the levels of antioxidant defense markers. These changes were assessed at baseline, 5 months, and 9 months through the analysis of plasma samples. However, the clinical trial was prematurely terminated at 21 months owing to the occurrence of treatment-related adverse events (Boll et al., 2014). Findings derived from three randomized trials revealed that although lithium did not improve the overall 12-month survival rate in the general ALS population, it significantly raised the 12-month survival probability from 40.1% to 69.7% among individuals carrying the UNC13A variant (van Eijk et al., 2017). Further investigations delving into the molecular mechanisms by which lithium operates with respect to ER stress, UPR, and autophagy may unveil potential neurobiological processes at play in the early stages of ALS, potentially leading to the identification of preventive or therapeutic targets.

E. Traumatic Brain Injury

TBI consists of an initial primary injury that causes mechanical damage to neurons, glia, and blood vessels. This primary injury is frequently succeeded by a sequence of secondary injuries that commence hours or even days following the initial trauma and that can lead to neurodegeneration as well as cognitive and motor impairments. TBI is also recognized as a potential contributor to the onset of neurodegenerative conditions such as AD. In fact, tauopathy and A β plaques are known to be the key pathologic markers of TBI, which contribute to the progressive deterioration associated with chronic traumatic encephalopathy and AD (Leeds et al., 2014; Shim and Stutzmann, 2016). Its pathophysiology requires pharmacologic agents that act coordinated

to increase cell survival and decrease cell death pathways. In this context, there is growing evidence to support the idea that lithium could potentially alleviate the neurologic impairments resulting from TBI by acting as an inhibitor of GSK3-mediated signaling (Leeds et al., 2014; Welling et al., 2017). Using murine models of TBI, lithium was reported to attenuate hippocampal neurodegeneration, IL-1 β expression, and brain edema. It also inhibits microglia activation, matrix metalloproteinase-9 expression, and cyclooxygenase-2 induction (Reis et al., 2015; Dell'Osso et al., 2016). In addition, low doses of combined lithium and valproate were more helpful in attenuating TBI than either agent used alone, leading to a reduction in neurodegeneration and neuroinflammation associated with improved behavioral outcomes (Yu et al., 2013). Zhu et al. (2010) achieved comparable outcomes, demonstrating that the administration of lithium led to a decrease in tissue damage while enhancing memory performance and spatial learning abilities. In addition, these data were associated with a decreased proinflammatory IL-1 β expression (Zhu et al., 2010). Likewise, lithium treatment was reported to reduce depressive-like behavior in mice after cold-induced TBI (Ciftci et al., 2020). Although not strictly a traumatic brain injury, lithium has been shown to be neuroprotective in people with cancer receiving chemotherapy or radiotherapy (Khasraw et al., 2012).

These discoveries suggest the potential repurposing of mood stabilizers like lithium and valproate, whether used individually or in combination, as viable pharmaceutical options for addressing neurologic disorders characterized by excitotoxic components, the best example of which is TBI. Currently, a phase 3 study (clinicaltrials.gov identifier: NCT05126238) examines the hypothesis that preoperative lithium administration may reduce brain damage during carotid artery surgery.

F. Stroke

Ischemic stroke is a severe life-threatening disease that causes degeneration and death of neurons, leading to the loss of motor function and frequent occurrence of cognitive impairment and depression (Pendlebury and Rothwell, 2009; Brown et al., 2012; Makin et al., 2013). The intricate pathophysiology of this condition encompasses an initial acute stage, during which neuronal loss is induced by a combination of hypoxia and nutrient deprivation. These factors set in motion mechanisms that ultimately give rise to neuroinflammation and apoptosis. The subsequent phase, marked by delayed brain injury, is further compounded by the subsequent restoration of blood vessel perfusion. Improving neurologic outcomes after an ischemic stroke is a major clinical priority. However, most neuroprotectants for stroke effective in rodent research have not been efficacious in clinical practice (Haupt et al., 2021; Chen et al., 2022a). Therefore, repurposing market-approved neuroprotective drugs, such as lithium, for

treating cerebral ischemia represents a viable strategy. In this context, previous studies using rodent models of stroke showed that lithium treatment induces antiapoptotic mechanisms, leading to decreased caspase-3 activity, reductions in activated protein one and proapoptotic p53 expression, and increases in antiapoptotic Bcl-2 and heat shock protein 70 (HSP70) levels (Xu et al., 2003; Bian et al., 2007). Furthermore, lithium enhanced hippocampal neurogenesis in a preclinical model of global cerebral ischemia. The effects, as mentioned earlier, are not both dependent on the GSK3 β pathway and involve other signaling pathways, such as prosurvival MAPK/ERK1/2 (Yan et al., 2007a,b; Sawe et al., 2008).

Further research endeavors were undertaken to explore the therapeutic potential of administering lithium following a stroke event. In a rat ischemia/reperfusion model, poststroke lithium treatment demonstrated a notable reduction in infarct volume and a corresponding decrease in neurologic deficits (Ren et al., 2003). Moreover, this neuroprotective effect was correlated with a decrease in apoptosis levels and an elevation in HSP70 levels (Ren et al., 2003). In addition, lithium administration led to improved spatial learning and memory performance in mice subjected to ischemia-reperfusion (Fan et al., 2015). Although the precise mechanisms governing how lithium regulates inflammation, apoptosis, and neuroplasticity after a stroke are still largely shrouded in mystery, emerging evidence hints at the possibility that lithium may exert its influence not only within the brain parenchyma but also directly on the endothelium itself (Bosche et al., 2016). Consistent with this observation, Haupt et al., (2020) reported that lithium-induced impact on endothelium cells could reverse early blood-brain barrier breakdown after stroke, resulting in a controlled modulation of leukocyte infiltration into the brain parenchyma. In addition to preclinical investigations, there is data from two clinical trials. One assessed retrospective risk in patients treated with lithium (Lan et al., 2015), and the other examined the prospective motor recovery of stroke patients undergoing lithium treatment (Mohammadianinejad et al., 2014). Thus, a randomized clinical trial on the effects of lithium in stroke patients demonstrated enhanced motor recovery after early treatment with low-dose lithium (Mohammadianinejad et al., 2014). More recently, however, evidence-based guidelines from the European Academy of Neurology and the European Federation of Neurorehabilitation Societies do not recommend lithium intervention for early motor rehabilitation after acute ischemic stroke due to safety and tolerability concerns (Beghi et al., 2021). Currently, some clinical trials (e.g., clinicaltrials.gov identifier: NCT05126238) aim to examine a lithium-based medication to improve neurologic outcomes after carotid artery surgery.

VIII. Limitations for Lithium Treatment

Despite its widely proven efficacy, lithium use is sometimes limited due to its narrow therapeutic index requiring routine monitoring of serum concentrations, possible negative effects on endocrine and renal function, or teratogenicity (McKnight et al., 2012).

A. Renal Function

Nephrogenic diabetes insipidus is the most common renal side effect of lithium therapy, characterized by loss of the ability of the kidney to concentrate urine due to resistance to vasopressin (Garofeanu et al., 2005). Rarely, when nephrogenic diabetes insipidus is uncontrolled, it may result in distal renal tubular acidosis (Weiner et al., 2014). Polyuria may rapidly occur during lithium treatment but is usually resolved once lithium is interrupted (Garofeanu et al., 2005). Long-term lithium treatment occasionally causes nephrotoxicity, characterized by kidney dysfunction and interstitial nephritis with microcyst formation and, occasionally, focal segmental glomerulosclerosis (Grünfeld and Rossier, 2009). In a longitudinal recent study on a large population of patients treated with lithium or valproate, results showed that lithium was meaningfully associated with adverse kidney outcomes, but the absolute risks did not significantly differ from those observed with valproate therapy (Bosi et al., 2023). However, the risk of chronic kidney disease increased with lithium levels >1 mmol/L (Bosi et al., 2023). In line with this evidence, another study showed that long-term lithium therapy was not linked to nephrotoxicity in the absence of acute intoxication episodes (Clos et al., 2015) nor to increased rates of chronic kidney disease (Kessing et al., 2015).

Although the biologic underpinnings of nephrotoxicity are complex and poorly understood, several molecular mechanisms might be implicated, including the suppression of phosphatidylinositol (3,4,5)-trisphosphate (PIP3) signaling, inhibition of GSK3 α , competition with magnesium ions, and overactivity of cyclooxygenase-2 (Gong et al., 2016).

B. Thyroid and Parathyroid Function

Thyroid (Kibirige et al., 2013) and parathyroid (Meehan et al., 2018) abnormalities affect up to 25% of patients receiving lithium treatment. Lithium is highly concentrated in the thyroid glands and inhibits iodine uptake, iodothyrosine coupling, and thyroxine secretion and modifies thyroglobulin structure (Pérez-Castro et al., 2021). Lithium competes for the iodide transport in thyroid glands, ultimately leading to reduced iodine reuptake (Shopsin et al., 1973). Lithium may also increase the thyroid-stimulating hormone secretion in response to the inhibitory effect on thyroxine (T4) availability, which leads to the inhibition of cAMP and alteration of tubulin polymerization (Lazarus, 1998). The alteration of thyroglobulin structure might be

caused by the effect of lithium on protein conformation and subsequent iodotyrosine coupling defects (Lazarus, 1998). These molecular alterations result in clinical manifestations such as hypothyroidism, goitre, or hyperthyroidism (Pérez-Castro et al., 2021). The risk of developing hypothyroidism and subclinical hypothyroidism in long-term treated patients is 6 times higher than in the general population (McKnight et al., 2012). Lithium-induced hyperthyroidism is less frequent and is characterized by transient and painless thyroiditis. The risk of developing primary hyperparathyroidism during lithium treatment is relatively high, and it is probably caused by the inactivation of the calcium-sensing receptor and interference with intracellular second messenger signaling, with a subsequent increase in parathyroid hormone and blood calcium levels (Szalat et al., 2009). Therefore, both thyroid and parathyroid function should be monitored in clinical practice by baseline blood tests of thyroid-stimulating hormone and calcium and regular yearly follow-ups (Malhi et al., 2017).

C. Lithium and Pregnancy

Clinical concerns have been raised regarding the risk of lithium during pregnancy. A recent meta-analysis showed that lithium-exposed women had higher odds of any congenital anomaly or cardiac malformations compared with nonexposed ones (Fornaro et al., 2020). However, the risk of congenital malformations at any time during pregnancy was globally low, being higher for the first trimester or with higher lithium doses. Also, there are no significant differences in obstetric outcomes in women with BD that take lithium during pregnancy compared with those not treated with lithium except for an impact on newborn Apgar scores (Sagué-Vilavella et al., 2022). However, although lithium treatment in the peripartum period is considered safe, attention should be paid during the first trimester in particular, always prioritizing the lowest effective dose (Clark et al., 2022).

D. Metabolic Effects

Weight gain is a distressing adverse effect that has been previously associated with lithium treatment (Gitlin, 2016). Lithium might have an insulin-like effect on increasing glucose uptake and glycogen production in animal models (de Groot et al., 2017; Jung et al., 2021). In humans, the administration of lithium induces insulin-like hypoglycemia (Shah et al., 1986). Likewise, lithium induces the suppression of GSK3, a key regulator of glycogen metabolism cell proliferation on differentiation (Snitow et al., 2021). However, a recent meta-analysis did not show a significant increase in weight in patients taking lithium compared with the ones without lithium or against placebo (Gomes-da-Costa et al., 2022). Indeed, patients with BD have a higher risk compared with the general population of developing weight-related conditions, including metabolic syndrome, diabetes, or obesity, independently of lithium treatment

(Prillo et al., 2021). A combination treatment with lithium antipsychotics is often used both in the acute and maintenance phases of BD. Antipsychotics, in particular olanzapine and clozapine, induce more pronounced metabolic side effects compared with lithium, including weight gain (Pillinger et al., 2020). Aripiprazole showed no significant differences in the long-term use compared with lithium in terms of metabolic parameters in patients with BD type I (McIntyre et al., 2011). When used in combination with antipsychotics, lithium showed to improve manic symptoms but also increase the risk of metabolic syndrome (Köhler-Forsberg et al., 2023).

E. Skin and Hair Disorders

There is conflicting evidence on the risk of skin and hair disorders with lithium treatment. Mechanisms involved in lithium-related skin disorders might involve cAMP cascade or the inhibition of the synthesis of prostaglandins, which ultimately stimulates neutrophil function (Jafferany, 2008). Although recent meta-analyses do not point to an increased rate of adverse skin reactions, clinicians should not overlook cutaneous symptoms during lithium treatment (Pinna et al., 2017).

F. Cognitive Effects

Concerns regarding cognitive impairment in patients treated with lithium have been raised (Wingo et al., 2009). Accumulating evidence is somewhat contrasting, suggesting that the cognitive effects of lithium are nuanced or showing a positive effect of lithium on cognitive performance. Some studies have indicated that lithium treatment may not only preserve but potentially improve certain aspects of neurocognitive function in individuals with BD (Burdick et al., 2020). Notably, cognitive domains such as verbal learning, memory recall, and executive functions (Rybakowski et al., 2009) have been found to exhibit positive responses to lithium therapy. However, individual responses may vary, and some patients may report subjective experiences of cognitive numbness (Grandjean and Aubry, 2009). Despite these reports, lithium's overall cognitive effects seem to lean toward benefiting neurocognitive functioning in patients with BD, further supporting its continued use as a valuable treatment option with careful monitoring and management of side effects.

G. Toxicity in Overdose

Lithium is dangerous in overdose, and clinical signs of toxicity might be seen at lithium serum concentrations equal to or more than 1.5 mEq/L (Oruch et al., 2014). Symptoms and signs of lithium toxicity may involve different systems, such as the gastrointestinal (nausea, vomiting, diarrhea), neurologic (confusion, lethargy, seizures, and coma, named syndrome of irreversible Lithium-Effectuated Neurotoxicity and attributed to cerebellar dysfunction), musculoskeletal (tremor or muscle

twitching), renal (renal failure), cardiovascular (T wave inversion, conduction disturbances, arrhythmias, atrio-ventricular node dissociations, cardiovascular collapse), and hematologic (leukocytosis) systems. Indeed, clinical guidelines suggest monitoring serum lithium concentrations regularly to avoid lithium overdose (Malhi et al., 2017).

Lithium's adverse effect and toxicity profile might be one of the causes of its decreased clinical usage during the last decade. The majority of side effects under lithium treatment are not life-threatening and can be easily managed.

IX. Conclusions and Future Directions

In this review, we focused on the multiple functions of lithium that demonstrate its exceptional pharmacology and therapeutic effects to highlight common mechanisms of action in different brain disorders. As the complex therapeutic mechanisms of lithium are unraveled, valuable information is provided to better understand the pathophysiology of the diseases in which it is implicated and point to possible new therapeutic developments. Converging evidence from preclinical and clinical models firmly supports the concept that lithium exerts regulatory effects on diverse cellular pathways within the brain that are crucial for neuroplasticity and neuroprotection. These include neurotrophic response, ER stress, UPR, autophagy, oxidative stress, mitochondrial function, and inflammation. This wide range of intracellular responses may be secondary to two key effects: inhibition of GSK3 and IMPase by lithium, in which dysregulation has been implicated in diverse neuropathological conditions. Therefore, a more profound and precise understanding of the specific therapeutic mechanisms of lithium will aid us in establishing a better understanding of the complex mechanisms underlying the pathophysiology of BD.

Although the promotion of autophagy is widely recognized as the primary molecular mechanism explaining lithium's protective effects in neurodegenerative diseases, there is still a lack of understanding regarding how lithium's ability to enhance autophagy might contribute to therapeutic benefits for patients with neuropsychiatric disorders, including BD. An inability to effectively clear misfolded proteins through autophagy can result in the accumulation of these substrates within cells. Consequently, a shared pathogenic factor implicated in neurodegenerative disorders is the inhibition of autophagy, often stemming from mTOR activation. However, the signaling pathway of lithium as an autophagy enhancer might be an mTOR-independent pathway involving IP3 signaling. Indeed, although the pathophysiology of neurodegenerative diseases is clearly different from mood disorders, cognitive impairment and functional decline are present in many bipolar patients, and neuroimaging findings confirm decreased neuroplasticity and its anatomic

correlates, particularly concerning gray matter loss (Vieta et al., 2018).

Although lithium unquestionably demonstrates efficacy in both treating and preventing BD, it is worth noting that certain subtypes of the disorder exhibit a reduced responsiveness to lithium, and not all individuals experience the therapeutic advantages it offers. The crucial task of pinpointing biologic indicators that can predict a patient's response to lithium remains a significant stride toward advancing personalized medicine in the treatment of BD (Salagre and Vieta, 2021).

With contemporary neuroimaging methodologies at our disposal to explore the fundamental neurobiological processes involved in BD, as well as the neuroprotective and neurotrophic impacts of lithium, there is a hopeful expectation that forthcoming research in neuroimaging will expedite the discovery and exploration of biologic indicators for predicting the response to lithium treatment. The development of more robust and personalized predictive models remains an important area of future research. Integrating multiomics data, such as genomics, transcriptomics, proteomics, and metabolomics with clinical characteristics, and other relevant factors through machine learning and artificial intelligence algorithms could significantly enhance the accuracy and specificity of such models. Also, innovation in molecular technologies, such as organ-on-a-chip systems and iPSC-derived three-dimensional organoids, can provide novel experimental models to study lithium's effects on human brain cells with greater precision and relevance. International collaborative consortiums involving different populations will be fundamental in generating comprehensive datasets for training and validating these models, therefore increasing their reliability.

The fact that lithium has withstood several tests, including concerns about its potential lethal toxicity and difficulty of use, and has remained steadfast as the treatment of choice for BD for more than six decades demonstrates that lithium is an essential therapeutic agent and an extraordinary tool in neuroscience research.

Data Availability

The authors declare that all the data supporting the findings of this study are contained within the paper.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Bortolozzi, Fico, Berk, Solmi, Fornaro, Quevedo, Zarate, Kessing, Vieta, Carvalho.

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