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REVIEW ARTICLE

What is the Role of Lithium in Epilepsy?

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Abstract: Lithium is a well-known FDA-approved treatment for bipolar and mood disorders. Lithium has been an enigmatic drug with multifaceted actions involving various neurotransmitters and intricate cell signalling cascades. Recent studies highlight the neuroprotective and neurotrophic actions of lithium in amyotrophic lateral sclerosis, Alzheimer's disease, intracerebral hemorrhage, and epilepsy. Of note, lithium holds a significant interest in epilepsy, where the past reports expose its non-specific proconvulsant action, followed lately by numerous studies for anti-convulsant action. However, the exact mechanism of action of lithium for any of its effects is still largely unknown. The present review integrates findings from several reports and provides detailed possible mechanisms of how a single molecule exhibits marked pro-epileptogenic as well as anti-convulsant action. This review also provides clarity regarding the safety of lithium therapy in epileptic patients.

Keywords: Lithium, seizures, epilepsy, lithium-pilocarpine model, inflammation, glycogen synthase kinase-3β (GSK-3β).

1. INTRODUCTION

Lithium (Li), a naturally occurring element, remains a gold standard drug for the treatment of bipolar disorders. It has had a fascinating and contentious history since its discovery in 1817. In the late 19th century, few physicians independently reported the therapeutic benefits of Li in treating acute maniac illness, which became obscure later. Again, in the mid-20th century, the anti-maniac effect of Li was reconsidered by John Cade, which led to several small numbered patient trials [1]. However, the lack of proper scientific methodology of trials, unknown mechanisms for its beneficial effect, and, more importantly, its toxicity owing to a narrow therapeutic index led to its failure in gaining approval [2-4]. After randomized placebo-controlled studies and the advancement of therapeutic drug monitoring, Li received FDA approval for acute mania relief and its prophylaxis in 1970 (Table **1**). Besides the anti-maniac effect, Li showed remarkable anti-depressive properties and gained immense recognition as a mood-stabilizing agent in bipolar patients [5]. The dose of Li is titrated to achieve serum concentrations of the range 0.5/1.2 mEq/L in acute and 0.5/0.8 mEq/L in chronic, 10-14 h after the last dose [6].

In addition to the cardinal mood-stabilizing action, many studies highlight the neuroprotective effect of Li in neurological diseases such as Alzheimer's Disease (AD) [15], Parkinson's Disease (PD) [16], intracerebral hemorrhage [17], epilepsy [18], and Amyotrophic Lateral Sclerosis (ALS) [19]. However, the mechanisms behind its pharmacological actions remain partially understood, primarily because Li has a multifaceted mechanism of action. It causes direct or indirect inhibition of proteins involved in various cell signalling pathways such as Glycogen Synthase Kinase-3 β (GSK-3β), phosphatidylinositol, N-methyl-d-aspartate/ nitric oxide/ cyclic-GMP (NMDA/NO/cGMP) [20] and also

Table 1. Key milestones in the history of lithium therapy.

Year	Important Events
1847	Gout [7]
1871	Prescribed for mania for the first time [8]
1894	Used for treating depression [9]
1949	The revival of lithium for mania [10]
1951	A first clinical trial of lithium in mania and many trials in Europe since then [11]
1960	Introduced in the United States [12]
1967	First time for depression [13]
1970	FDA approved for acute maniac illness [5]
1975	Prophylaxis of mania [14]

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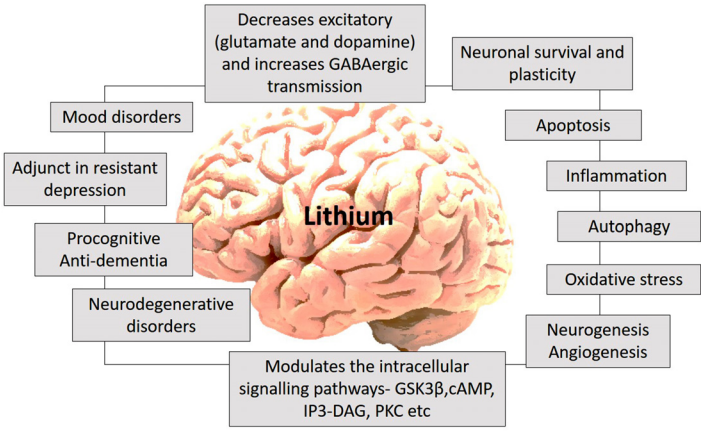

Fig. (1). Pleiotropic effects of lithium in various neurological disorders. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

exerts differential influence over multiple neurotransmitters such as acetylcholine, norepinephrine, glutamate, dopamine, *etc*. [21]. The multifaceted action of Li (Fig. **1**) can be due to its ionic size. Li is the smallest monovalent cation, followed by sodium, and shares identical ionic and atomic radii with that of a divalent cation, magnesium, a physiologically key ion. Therefore, in the body, Li competes with magnesium and less likely with sodium by measures of size and charge. Most biological actions of Li can be reasoned with the result of this competition [22]. It is well known that sodium, magnesium, and calcium ions are the basis for cellular functions and life. Henceforth, the range of targets of Li is broad, including neurotransmitters, receptors, second messengers, kinases, transcription factors, and genes.

Li has a narrow therapeutic index ranging between 1.5-1.6 mEq/L and hence is recommended for regular therapeutic drug monitoring. For bipolar disorders, generally, serum levels of 0.5-0.8 mEq/L are achieved for the treatment. Kidneys excrete Li as a free ion, thus needs to be used cautiously with renal impaired and geriatric patients [23]. Serum levels higher than 1.5 mEq/L produce mild symptoms such as tremors, nausea, vertigo, confusion, and a few persistent neurological deficits. Serum levels above 2.5 mEq/L result in severe neurological adverse effects such as seizures, coma, and permanent neurological impairment [24].

The role of lithium in epilepsy is of particular importance because a significant proportion of epileptic patients suffer from psychiatric comorbidities such as anxiety, depression, postictal mania, psychosis, and other mood disorders [25]. Anti-epileptic drugs such as phenytoin, carbamazepine, barbiturates, *etc.*, can also cause mania after prolonged use or during the withdrawal phase [26]. Anti-depressants, anti-psychotics, and Li are the available therapeutic options for treating bipolar disorders and associated mood disorders. However, some of these drugs are claimed to have convulsive properties, hence need to be avoided (*e.g.*, tricyclic anti-depressants) or used moderately with caution (lithium) in epileptic patients [27, 28].

Notably Li is considered to be proconvulsive and is also shown to cause electroencephalogram (EEG) abnormalities in patients. In addition, Li caused encephalopathy in carbamazepine-treated patients [29]. Even then, Li was safely used in epileptic patients to treat affective disorders, and it stays as a secondary drug of choice, often as an adjunct [30]. With this background, it is essential to systematically identify the safety and role of lithium in epilepsy. Therefore, in this review, the mechanisms responsible for both the pro-convulsant and anti-convulsant actions of Li will be discussed to understand how an ion modulates the neurochemistry of the brain and shows effects so wide apart.

2. METHODS

An extensive literature survey was carried out in PubMed, Scopus, and Web of Science using appropriate keywords. Published articles that addressed the review objective were discussed and reviewed. All kinds of scientific evidence were obtained, including case reports and controlled studies. The bibliographies of the obtained papers were also manually searched for additional relevant articles. The search was limited to the English language. There was no date limit, and the last search was conducted in June 2021.

3. LITHIUM AS PRO-CONVULSANT

Several case reports and anecdotal clinical evidence demonstrate the incidence of different kinds of seizures, such as generalised tonic-clonic, myoclonic, and Nonconvulsive Status Epilepticus (NCSE) in patients treated with Li [4, 5, 25-27]. This can be partly explained by the dose-dependency. When serum levels of Li exceed the therapeutic range, *i.e.*,> 1.5 mmol/l, an association between NCSE and Li intoxication was observed [31, 32]. A plasma level of Li greater than 2.5 mEq/L is reported to be associated with neurological problems, which include seizures, coma, nausea, vertigo, and dizziness [34]. However, patients with serum levels of lithium within the therapeutic range, *i.e.*, 0.45/0.60 and up to 0.80/1.00 mmol/L, have also shown NCSE with no systemic signs of toxication [33]. Chronic treatment with Li levels, even at 0.58 mmol/L, also revealed similar findings with an increase in seizures, behavioural abnormalities, and EEG-related pathology in temporal epileptic patients [35]. The possible explanation could be that serum Li concentrations do not necessarily reflect brain concentrations, and Li does not distribute uniformly over different regions of the brain [35].

Of note, Li is widely employed as a proconvulsant to potentiate pilocarpine in order to generate status epilepticus (SE) in experimental animals [36, 37]. Pilocarpine is an M1

Table 2. Studies indicating proconvulsant action of lithium.

S. No.	Study Design	Inference	Study References
1.	Chronic Li 3 mEq/kg in the diet for 22 days in the amygdala kindling model	No effect on seizure development	[128]
2.	Acute Li at 0, 0.25, 0.5, 1.5, 3.0, or 5.0 mEq/kg i.p. in hippocampal kindling in rats	Seizure threshold and severity unaffected. After discharge duration (ADD) significantly prolonged at the 3 mEq/kg dose ($p < 0.04$).	[129]
3.	Chronic lithium administration (2.2-8.7 mEq/kg/day, 17 days) to the cat using the low-frequency kindling technique	Li 4.3 mEq/kg/day PO caused an elevation of the amygdala seizure threshold on treatment days 5-9	[130]
4.	LiCl 3 mmol/kg, 20 h prior to pilocarpine, arecoline or physostigmine	Potentiates the proconvulsive effects of cholinomimetics	[131]
5.	Chronic LiCl (1.70 – 2.55 g/kg in diet) in rats	PLA2 mediated increased levels of arachidonic acid and its metabolites which upregulated glutamatergic transmission, neuronal excitability, and seizure propagation	[79]
6.	Acute Li 3 mEq/Kg in healthy rats	Abnormal EEG activity characterized by mild synchronous bursting 3 hours post-administration and conspicuous synchronous 4-5 Hz theta activity with unilateral spikes of increased amplitude at 20 hours post-administration	[40]

muscarinic acetylcholine receptor agonist commonly used to induce seizures in rodents. Treatment with Li chloride (3mEq/kg or 127 mg/kg, i.p.) 19-21 h before pilocarpine reduces the dose of pilocarpine 10-13 fold (30 mg/kg, s.c. instead of 320 mg/kg, i.p.) needed to produce convulsive SE. The high dose pilocarpine (320 mg/kg) and Li-pilocarpine (Li-Pi) models produce identical disease pathology. Primarily, these models generate SE followed by an epileptogenic latent phase that leads to temporal lobe epilepsy characterized by Spontaneous Recurrent Seizures (SRS). However, the Li-Pi model offers several advantages, such as reduced mortality and variability in producing SRS [36].

Based on these clinical and preclinical pieces of evidence, the proconvulsant action of Li is evident (Table **2**). The mechanisms that seem to drive its pro-convulsant effects are discussed below.

3.1. Increasing the Excitatory to Inhibitory Ratio

Li increased brain excitability by increasing the net excitation to inhibitory ratio. Acute Li showed a dose-dependent progression of normal synchronous neuronal activity (<1 mM) to an increased epileptiform-like discharge (> 1mM) in Human-induced Pluripotent Stem Cell (iPSC) derived cortical neuronal models. It clearly showed an increase in neuronal activity as well as neuronal excitability with overdoses of lithium by increasing the AMPA receptor Excitatory Postsynaptic Currents (EPSCs) frequency [38]. However, chronic Li treatment decreased action potential frequency in human iPSCs [39].

Accordingly, single-dose LiCl (3 mEq/Kg) in rats caused abnormal EEG activity characterized by mild synchronous bursting three hours post-administration and conspicuous synchronous theta activity with unilateral spikes of increased amplitude at twenty hours post-administration. This abnormal EEG activity can be correlated with the decreased seizure threshold observed in patients with Li therapy. Notably, Li alone did not produce electrographic seizure activity, whereas a sub convulsive dose of pilocarpine along with Li pre or post-treatment initiates limbic seizure activity that progresses to generalized tonic-clonic seizures in rats [40].

3.2. Potentiating the Cholinergic Transmission

Acetylcholine is a major excitatory neurotransmitter that mediates its effects through muscarinic receptors (M1-5) located on pre and postsynaptic cholinergic and non-cholinergic synapses in the brain. The cholinergic transmission plays a critical role in the normal physiology of temporal lobe structures, a prime accused region for developing epilepsy and seizures [41]. Conditions with enhanced neuronal activation, such as seizures, cause increased acetylcholine levels, enable transcription of cholinergic genes, and alter the key proteins determining the cholinergic functions [42]. Cholinomimetics such as pilocarpine at high doses can initiate seizures through muscarinic M1 activation, which progresses to SE. In addition, pilocarpine does not produce seizures in M1 knockout mice, proving that M1 receptors mediate neuronal excitability [43]. M1 activation leads to a rise in intracellular Ca^{2+} level through multiple sources such as the activation of glutamate receptors, opening of calcium channels in response to membrane depolarization, and release from intracellular stores in response to secondary messengers leading to excitotoxicity. Again, this is site-specific, with entorhinal cortex cells more vulnerable to Ca^{2+} build-up than layer II cortical cells. In addition, this muscarinic-induced hyperexcitability is associated with abnormal gene expression, which can be reversed by Ca^{2+} chelators [44].

Li is a critical component of the Li-Pi model, a reliable and widely utilized animal model to generate SE, which progresses towards temporal lobe epilepsy. The marked epilep-

togenic action of Li is associated only with cholinomimetics such as pilocarpine and arecoline, and acetylcholinesterase inhibitors, physostigmine [45], which indicates that it enhances the endogenous acetylcholine activity. Supporting this, a 6-fold increase in hippocampal acetylcholine levels is observed in these animal models upon lithium treatment [46].

Li has also shown partially enhanced choline transport, which boosts acetylcholine synthesis and directly potentiates the postsynaptic muscarinic receptors [47]. Several studies reveal that Li influences the cholinergic system by affecting the muscarinic receptor binding affinity and receptor signalling pathways [48]. However, the exact mechanisms and the magnitude by which Li influences cholinergic transmission are unknown. Furthermore, clinical evidence of the effect of lithium on CNS cholinergic transmission is available. However, in the periphery, Li has also been shown to increase the choline content of RBCs by inhibiting its efflux in bipolar patients [49].

3.3. Altering the Phosphoinositide 3-Kinase (PI3K) Metabolism

Phosphoinositides (PI) regulate key subcellular processes, including calcium homeostasis, membrane transport, cytoskeletal function, *etc.* Phosphatidylinositol 4,5-bisphosphate (PIP2) hydrolysis by phospholipase C (PLC) generates secondary messengers, diacylglycerol (DAG), and inositol 1,4,5-trisphosphate (IP3), which leads to protein kinase C activation and Ca^{2+} mobilization [50]. Several phosphatases, such as myoinositol-l-phosphatase (IMPase), regulate the levels and, therefore, the activity of the molecules involved in the PI cycle. Li interferes in the metabolism of phosphatidylinositol at various places. The range can vary according to species, dose, and duration of treatment. Inhibiting the IMPase is the widely studied one, whereby it elevates the level of myoinositol-1-phosphate (MIP) and depletes the inositol pool. In the Li-Pi model of epilepsy, acute Li administration produced a 40-fold increase in MIP levels. In contrast, only a 4-fold increase was observed in the absence of lithium [51]. Similarly, inositol uptake inhibitors such as L-fucose and nordidemnin have minor but significant effects on seizures susceptibility in the pilocarpine model [52]. These studies indicate that the inositol depletion and/or phosphoinositol accumulation contribute to the enhanced seizure susceptibility upon acute Li treatment [53]. Supporting these observations, Kofman *et al.* showed that inositol administration could reverse the increased seizure susceptibility of Li pre-treatment in the Li-Pi model [54]. Li also potentiated pilocarpine's actions by increasing phosphoinositide signalling, where pilocarpine elevates MIP generation through M1 receptors in the hippocampus and cortex, and Li prevents MIP breakdown [55, 56].

3.4. Inhibiting the Noradrenergic Transmission

NE activity in the limbic system appears to be crucial in regulating epilepsy-induced neuronal alterations. Further, loss of NE promoted neuronal damage in limbic status epilepticus, supporting NE's protective role in neurological diseases [57]. Li alters noradrenergic activity by decreasing norepinephrine availability to adrenergic receptors. LiCl (2 mmol/kg, i.p.) increased the α adrenergic receptor affinity for norepinephrine reuptake and increased its turnover, thereby limiting its synaptic availability [58]. Few studies report that Li shows region-specific differential adrenoceptor binding, relatively more with β1, β2, and α1 receptors. Chronic oral administration of lithium downregulated the cortical but not cerebellar α and β adrenoceptors. α1-adrenoreceptors are positively linked to PLC, which cleaves PIP2 into DAG and IP3. Hence, Li-mediated downregulation of α1-adrenoreceptors decreased PLC activity and reduced the IP3 levels in the cortical tissue. On the other hand, α2 adrenoceptors negatively regulate cAMP. Hence, Li-mediated decrease in α2 adrenoceptors increased cAMP accumulation and decreased adrenergic transmission. It is possible that reduction in adrenergic transmission also favours cholinergic activity, which in turn can promote seizures [59].

In addition to directly affecting seizure susceptibility, LiCl also reduces the effect of anti-convulsant drugs such as phenytoin, phenobarbital, methazolamide, and acetazolamide. Kadzielawa showed that Li (50 mg/kg; i.p., three consecutive doses 12 h apart) inhibited the anti-convulsant efficacy of these anti-convulsants by increased intraneuronal deamination of dopamine and norepinephrine and antagonism to norepinephrine at the postsynaptic membrane [60]. These studies also support the partial involvement of dopamine and norepinephrine in the anticonvulsant action of these drugs.

3.5. Promoting the Peripheral Inflammation

Acute brain insults such as Traumatic Brain Injury (TBI), infections in the CNS, and stroke lead to the leaky Blood-Brain Barrier (BBB), which causes inflammation and contributes to epileptogenesis and seizures [61] Marchi *et al.* showed the involvement of inflammatory components in the pro-epileptogenic action of Li. Li (3 mEq/kg) administered 20 h before pilocarpine (30 mg/kg, i.p.) produced an abnormal EEG activity three hours before seizures in Sprague Dawley (SD) rats. This atypical brain theta activity corresponded to the surge in serum interleukin-β (IL-β) level and BBB damage. Li pre-treatment activated the peripheral immune cells, T-lymphocytes (mainly CD8), and mononuclear cells, which in turn rapidly release IL-1β in high amounts. Elevated serum IL-1β levels upregulate BBB adhesion molecules and compromise their selective permeability. This enhanced BBB permeability increases the pilocarpine delivery to the brain, thereby enhancing its convulsant activity even at minimal doses. Similarly, pilocarpine alone (350 mg/kg, i.p.) produced epileptic discharge with decreased peripheral T lymphocytes, decreased CD4:CD8 ratio, and high serum IL-β levels. Notably, the IL-β levels in the Li-Pi model were higher than in the pilocarpine (350 mg/kg) model. These results indicate the role of Li in IL-1β upregulation. Also, it points towards a common mechanism of inducing SE by Li and pilocarpine irrespective of the time of Li's administration (before or after pilocarpine administration). The increase in circulatory IL-β causes loss of cerebrovascular control of brain homeostasis (as in systemic infection), which is a major causative agent of seizures in the pediatric and adult population [40, 62]. Under *in vitro* conditions with hippocampal slice cultures, pilocarpine treatment produced epileptiform activity only at increased extracellular K+ concentration [63]. These studies indicate that the Li/pilocarpine induces a

peripheral inflammatory response comprised of increased serum IL-1β levels and altered BBB permeability, resulting in an influx of potassium ions in the brain that can cause epileptic discharge. In the *in vitro* study, lack of peripheral immune activation resulted in the absence of epileptic discharge, which was again induced upon elevated extracellular K+ concentration. Similarly, the presence of BBB permeability-enhancing agents such as bradykinin or histamine could induce epileptic discharges even at subthreshold doses of pilocarpine in both *in vitro* and *in vivo* conditions [40, 61, 62, 64]. Supporting this, chronic Li treatment (2.5 mEq/kg, i.p., six weeks) increased hippocampal BBB permeability in healthy rats [65]. BBB impairment causes albumin extravasation, which in turn activates the TGF-β signalling pathway leading to neuroinflammation [66].

In addition to the BBB leakage, Li pre-treatment produces several anomalous changes such as enlarged and asymmetric ventricles, reactive astrogliosis, *etc.*, particularly in limbic areas and the neocortex. So, it is conclusive that Li promotes epileptogenesis by enhancing BBB permeability and increasing brain pilocarpine concentrations [61].

Several reports show that patients treated with Li acutely or chronically exhibited increased white blood cell counts and neutrophils, even at therapeutic concentrations [67, 68]. Low dose Li is clinically used in neutropenia of several aetiologies such as chemo-induced, clozapine-induced, autoimmune induced, *etc.*, to increase the neutrophil and leukocyte count [69]. On the contrary, there are numerous studies where Li showed anti-inflammatory effects protected the BBB integrity during various insults such as ischemia [63], chronic mild stress [65, 70], and traumatic brain injury [71]. Further studies are needed for a clear understanding of the opposite effects exerted by Li on BBB permeability.

3.6. Inhibiting Cell Signalling Pathways/Secondary Messengers (IP3/Ca^{2+}/Arachidonic Acid/ GSK-3β)

3.6.1. IP3 and Ca^{2+} Signalling

Another mechanism by which LiCl has shown its proconvulsant action is by regulating secondary messengers, primarily IP3 and Ca^{2+}. In non-rodent species (guinea pig, rabbit, and rhesus monkey), Li (l-1.5 mM) increased the accumulation of IP3 in the cerebral cortex [72]. Further, IP3 upregulates the release of Ca^{2+} from the endoplasmic reticulum, increasing intracellular Ca^{2+} levels [73]. Elevated Ca^{2+} induces the release of acetylcholine from the presynaptic neurons, which increases excitatory postsynaptic current and causes seizures [74]. This is further confirmed with pregabalin, a Ca^{2+} channel blocker that reduced SE-induced damage by inhibiting Ca^{2+} influx in the Li-Pi model in SD rats [75].

It was also observed that Li increased the release of glutamate, which activated the N-methyl-D-aspartate (NMDA) receptors, and increased Ca^{2+} influx [72]. The increased Ca^{2+} influx activates phospholipase C and leads to the accumulation of IP3. High IP3 levels further emptied the Ca^{2+} stores and caused excitotoxicity. Li at a serum concentration greater than 1.5 mEq/L can be toxic by excessive glutamate release and hyperactivation of the NMDA receptors. Thus, Li does not regulate phospholipase C directly but by inducing the pre-synaptic release of neurotransmitters, such as glutamate or acetylcholine. It seems clear that Li mediates its effects by the modification of the calcium homeostasis or the receptor coupled secondary messenger amplification mechanism, which changes the functional behaviour of particular neurotransmitter systems.

3.6.2. Arachidonic Acid Pathway

Brain cells contain a high concentration of arachidonic acid (AA), a key component of brain function and structure. Ca^{2+}-dependent cytosolic phospholipase A2 (PLA2) hydrolyzes AA from synaptic membrane phospholipids, increasing unesterified fatty acids and lysophospholipids [76, 77]. Increased PLA2 activity was observed in the hippocampus of the pilocarpine model of TLE and the hippocampal samples of patients with TLE [77], leading to increased accumulation of lipid metabolites in the brain, causing seizures. Along with it, seizures also affect the metabolism of lipids such as AA in the brain, which leads to the 'seizure beget seizure' phenomenon [78]. Li has shown to promote pro-convulsant effect by phospholipase A2 (PLA2). Basselin *et al.* showed that LiCl (1.70-2.55 g/kg in the pelleted form) activated PLA2, which increased the release of arachidonic acid from the phospholipid membrane of auditory and visual regions of rats. The increased levels of arachidonic acid and its metabolites (eicosanoids) upregulated glutamatergic transmission and neuronal excitability and contributed to seizure propagation. Arecoline (2 and 5 mg/kg, i.p.), a cholinomimetic drug administration to the LiCl-fed rats, has increased the AA levels and promoted seizures [79].

3.6.3. GSK-3 Signalling

In addition to these secondary messengers, Li is well known to inhibit glycogen synthase kinase 3 (GSK-3). GSK-3 is an atypical kinase that is constitutively active and gets inhibited upon phosphorylation by upstream regulators such as Akt. It has a wide range of substrates, acting as a focal point in cellular signalling, intricately connected with multiple signalling pathways such as Wnt and insulin. GSK-3β, an isoform of GSK-3, regulates various cellular processes in CNS, such as cellular survival, inflammation, Long-Term Potentiation (LTP), and synaptic reorganization [80]. A recent study showed that increased GSK-3β decreases neuronal excitability through modulating levels of Hyperpolarization Activated Cyclic Nucleotide Gated Potassium Channel 4 (HCN4) and phosphorylation of AMPA receptor subunit, GluA1 [106]. Lithium exerts most of its pharmacological effects by GSK-3β inhibition. These are mediated through various mechanisms such as competitive inhibition of Mg^{2+} ion, inhibition of N-terminal serine phosphorylation, or upregulation of Akt activity [81-83]. Because of its wide range of cellular targets, global inhibition of GSK-3β can lead to severe side effects. GSK-3β inhibition plays a key role in Li therapy-induced neurotoxicity and other side effects. C57BL/6 mice fed with LiCl supplemented chow (1.7 g/kg for two weeks; followed by 2.55 g/kg for six weeks) showed gait abnormalities followed by increased neuronal apoptosis in many parts of the brain, including basal ganglia, striatum, and cortex mediated through GSK-3β inhibition. The study showed that GSK-3β inhibition upregulated the nuclear translocation of the Nuclear Factor of Activated T-cells (NFAT) transcription factor that induces the Fas ligand (FasL) expression, leading to extrinsic pathway-mediated apoptosis [83]. On the contrary, studies show that lithium

counteracts the intrinsic pathway of apoptosis and provides neuroprotection [84].

Further, the influence of GSK-3β over seizures and seizure-induced pathology was investigated in the intra-amygdala kainic acid-induced SE model in mice [85]. Both increased or decreased GSK-3β expression increased the seizure severity and pathology. SE exerted region-specific influence over GSK-3β transcription and phosphorylation in the hippocampus. Upregulated GSK-3β expression along with increased Ser9 phosphorylation was found in the CA1, the region with the least neuronal death. In contrast, the CA3 region having more SE-related neuronal death had decreased GSK-3β transcription. Overexpression of GSK-3β during SE upregulated the pro-inflammatory mediators through NF-κB activation and facilitated seizure-induced neuronal death through the intrinsic and extrinsic apoptotic pathways, resulting in increased brain damage and seizure severity. These results are indicative of the neuroprotective effect of GSK-3β inhibition. Surprisingly, overexpression of GSK-3β also resulted in the downregulation of the genes involved in synaptic transmission, and hence inhibiting GSK-3β facilitated the upregulation of genes involved in seizure generation. These results indicate that increased or decreased activity of the GSK-3β appears to produce negative effects in seizures [85].

4. ANTI-CONVULSANT ACTION OF LITHIUM

In contrast to the above-discussed proconvulsant mechanisms of Li, numerous studies and recent reports state the neuroprotective properties and less likely its anti-convulsant properties (Table **3**). Since 1948, Li has been used as a mood stabilizer in mania and depression, but the latest research is mainly focused on its neuroprotective and neurotrophic actions [86-88]. An observational study in 1028 adult psychiatric patients on Li therapy revealed fewer neurological problems such as dementia, ALS, and seizures in regular clinical practice [89]. Indeed, several clinical studies showed increased grey matter volume in bipolar patients treated with Li therapy which correlated with its therapeutic efficacy [90]. Emerging research suggests its neuroprotective effects, such as preventing apoptosis and neuronal atrophy, *etc.*, and neurotrophic effects, such as augmenting neuronal growth, proliferation, regeneration, differentiation, *etc.* [91]. Studies have reported neuroprotective action of low dose Li in cellular and animal models of epilepsy, AD, Down syndrome, Huntington's disease, PD, stroke, ALS, spinal cord injury, spinal muscular atrophy, neurodevelopmental disorders, and retinal degeneration [18, 92, 93]. Lithium treatment at therapeutic concentrations (0.6-1.25 mEq/L) showed either a reduction in seizures in the majority of the epileptic patients or a lack of effect in a few patients and rarely increased seizure activity [89, 94–97]. Li is also reported to increase seizure threshold in acute rodent models of seizures such as Maximal Electroshock (MES) and Pentylenetetrazol (PTZ), as well as in chronic models such as PTZ kindling and Li-Pi (post-treatment) [93, 98].

Main pharmacodynamic targets of Li include IMPase, GSK-3β, NMDA receptor-mediated Ca^{2+} influx, cAMP, cyclic adenosine monophosphate-responsive element-binding protein (CREB), and Na+/K+ -ATPase [99]. In particular, Li has been shown to inhibit GSK-3α and GSK-3β; upregulate neurotrophins and cell survival molecules (*e.g.*, Bcl-2, Brain-Derived Neurotrophic Factor [BDNF]/ tropomyosin receptor kinase B [TrkB], CREB, heat shock protein 70 [Hsp70], and β-catenin); downregulate proapoptotic activities (*e.g.*, excitotoxicity, p53, Bcl-2-associated X protein, caspases, cytochrome c release, β-amyloid peptide production, and tau hyperphosphorylation); inactivate NMDA receptors; inhibit IMPase, and activate the PI3K/Akt cell survival pathway [100]. Apart from this, Li exerts a direct modulatory effect on excitatory and inhibitory neurotransmission (dopamine/glutamate versus GABA) (Fig. **2**) [100]. Such a wide range of intracellular responses involved in the neuroprotective action of Li may be secondary to its inhibitory effect on two key broad targets, namely, GSK-3β and IMPase. The following mechanisms are proposed to be involved in its anti-convulsant action.

4.1. Inhibiting NMDA Receptor-Mediated Ca^{2+} Influx/Glutamate Excitotoxicity

Noxious stimuli such as seizures cause excessive glutamate release, causing overactivation of glutamate receptors (NMDA, AMPA, metabotropic glutamate), leading to enormous intracellular Ca^{2+} accumulation. These cellular changes lead to secondary events such as the generation of reactive oxygen species (ROS), nitrosative stress, endoplasmic stress, mitochondrial dysfunction, caspase activation, and intracellular organelle dysfunction, which ultimately result in cell death [101]. Li is shown to inhibit the NMDA receptor activation and prevent the intracellular rise in Ca^{2+} concentration, thereby inhibiting the downstream activation of phospholipases, protein kinase C, and Nitric Oxide Synthase (NOS), resulting in neuroprotective effects and anti-convulsant effects [93]. In similar lines, pre-treatment of Li for seven days showed protection against NMDA-induced excitotoxicity in hippocampal neurons, cerebellar neurons, and cerebral cortex [98, 102, 103]. Post-treatment of Li exhibited anti-convulsant and neuroprotective effect in pilocarpine-induced seizures in C57BL/6 mice by inhibiting the NMDA receptor-mediated Ca^{2+} influx. Administration of acute dose of LiCl (80 mg/kg, i.p.) 15 min after pilocarpine injection (320 mg/kg, i.p.) delayed the seizure onset and reduced mortality; besides reducing hippocampal neuronal damage (neuroapoptosis) with no effect on glial activation [98]. Further, acute Li treatment exhibited dose-dependent (5-100 mg/kg, i.p.) anti-seizure activity in PTZ induced seizure model. It also displayed a synergistic activity with calcium channel blockers (nifedipine, verapamil, and diltiazem) and NMDA receptor antagonists (ketamine and MK-801) [104]. Altogether these observations suggest the involvement of NMDA and Ca^{2+} in the anti-convulsant role of Li. Supporting these findings, a plethora of evidence is available where Li protects the neurons from glutamate-induced excitotoxicity in neurodegenerative diseases and *in vitro* models [105]. Li at lower doses than that of therapeutic concentrations reduced the tyrosine phosphorylation (Tyr1472) of the NR2B subunit of NMDA receptors, and this reduction correlated with the decreased Ca^{2+} influx and neuroprotective effect in the cerebral cortex [102]. Try1472 phosphorylation is essential for the NMDA receptor function as it inhibits the receptor internalization and increases its surface availability. Try1472 phosphorylation is elevated during the long-term potentiation occurring in hippocampal CA1 regions. PKC activators increase this phosphorylation, and PKC inhibitors

Table 3. Studies indicating anti-convulsant action of lithium.

S. No.	Model/Study	Major Finding	Study References
1.	LiCl single dose (25 mg/kg) in the PTZ model in NMRI mice	Activating the NO-cGMP pathway and increasing the seizure threshold	[88]
2.	Acute and 7 days long (chronic) LiCl pretreatment (10, 20, 30, 60 mg/kg; i.p.) in PTZ induced clonic seizure model	Through Phospho ERK/NMDA receptor/NO signalling reduced the glutamate neurotoxicity	[93]
3.	LiCl (0.05 mg/kg); (PTZ)-induced clonic seizure in mice.	Inhibition of NO (secondary messenger) mediated the anti-seizure effect of LiCl	[111]
4.	LiCl (doses more than 5 mg/kg) after 30 min in PTZ-induced seizure model in mice (PTZ, 0.5%; 1 mL/min)	NMDA/nitrergic pathways mediated the anti-seizure effect of LiCl	[122]
5.	LiCl (80 mg/kg, i.p.) in C57BL/6 mice after Pilocarpine injection (320 mg/kg, i.p.)	Delayed the seizure onset and reduced mortality; reduced hippocampal neuronal damage through inhibition of NMDA receptor-mediated Ca^{2+} influx.	[98]
6.	Li (400 mg extended-release (ER) in a clinical study in Ring chromosome 20 disorder patients	Improved epilepsy and behavioural symptoms possibly by Inhibiting KCQN2 channel phosphorylation through a) inhibiting GSK-3β b) inhibiting IMPase	[96]
7.	LiCl (30 mg/kg; i.p.) in NMRI mice in PTZ acute seizure model	increased the seizure threshold through α2-adrenergic signalling	[115]
8.	In vitro using rat cerebral cortical neurons Li (1mM, 5-6 days)	Protected from glutamate excitotoxicity by reducing tyrosine phosphorylation of NR2B subunit of NMDA receptor-mediated Ca^{2+} influx.	[102]
9.	Acute Li (5–100 mg/kg, i.p.) treatment in PTZ acute seizure model	Increases the clonic seizure threshold possibly through reducing Ca^{2+} signalling	[104]
10.	LiCl (10 and 80 mg/kg, i.p.) to pilocarpine-induced acute seizure model in male Sprague-Dawley rats	At 10 mg/kg, amplified hippocampal gamma and theta oscillations and decreased the duration, increased the latency of stage 4-5 seizures, and reduced the frequency of low stage seizures At 40mg/kg, decreased the hippocampal gamma and theta oscillations and increased seizure susceptibility	[18]
11.	LiCl (1.5 - 3 mEq/kg) for 16 days in Left middle cerebral artery (MCA) occlusion model in rats.	NMDA receptor inhibition	[103]
12.	LiCl (60 mg/kg, i.p. twice daily for 14 days) in hemorrhage model of stroke in Male SD rats	GSK-3β inhibition – leads to a. inhibiting downstream CRMP-2/NR2B b. stabilized β catenin and hence inhibited apoptosis-related factors	[17]
13.	LiCl (40 mg/kg or 80 mg/kg, i.p.) treatment in cancer curative treatment cranial irradiation in C57/BL/6J mice and SD rats.	Protected the neurons and inhibits the GSK-3β pathway and Bax protein synthesis. LiCl activated the phosphatidylinositol-3-kinase/Akt pathway, which inhibited the proapoptotic GSK-3β.	[122]
14.	LiCl (10 mM) treatment in human-derived microglial cells	LiCl induced GSK-3β phosphorylation and blocked nuclear translocation of transcription factors, STAT1 and STAT3 by dephosphorylating them, hence blocking the inflammatory kynurenine pathway in microglia.	[131]
15.	1028 adult male and female psychiatric outpatients on lithium therapy	Neuroprotective and cardioprotective effects in the patients	[89]

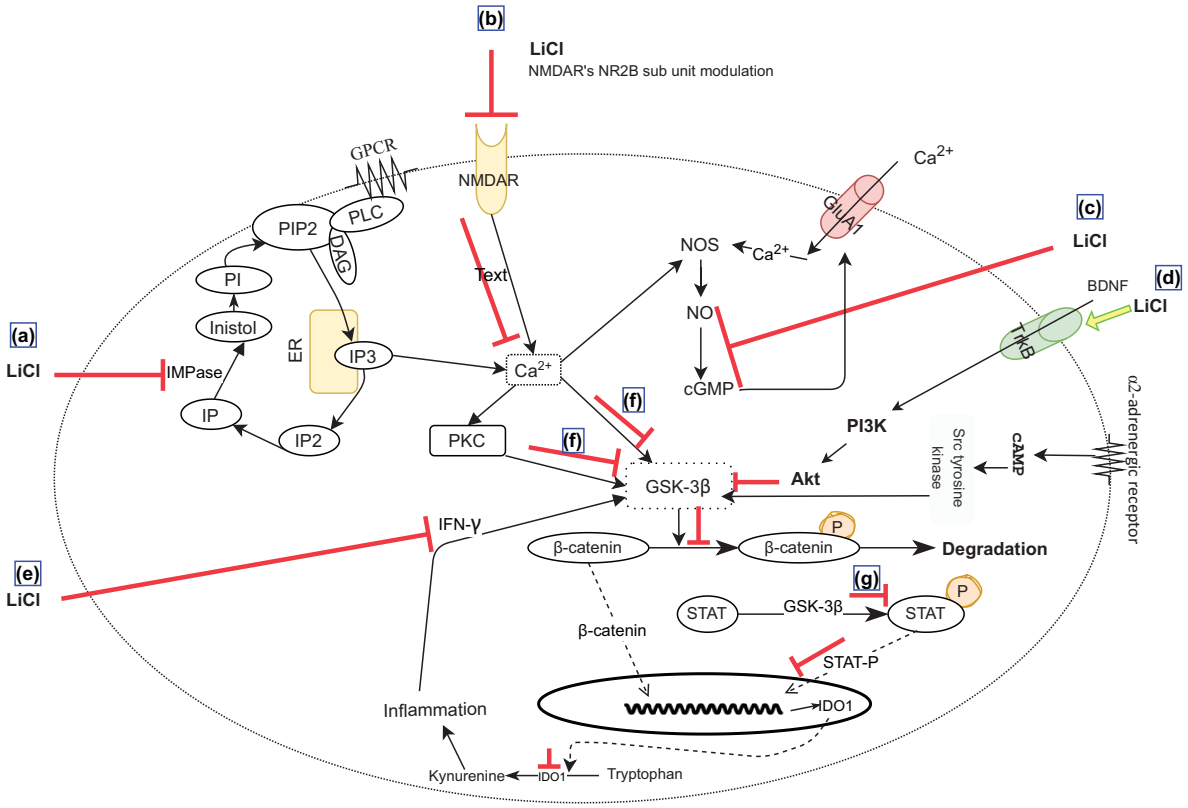

Fig. (2). Graphical representation of pathways involved in lithium mediated anti-convulsant and neuroprotective effect: **a**) LiCl inhibits inositol monophosphatase (IMPase) that downregulates IP3 mediated rise of intracellular Ca^{2+}. **b**) LiCl modulates the NMDA receptor 2B (NR2B) subunit and hence inhibits NMDAR mediated Ca^{2+} influx. **c**) LiCl inhibits Nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) cGMP pathway, which inhibits Glutamate ionotropic receptor AMPA type subunit 1 (GluA1) receptor-mediated Ca^{2+} inflow. **d**) LiCl stimulates BDNF/TrkB mediated Akt pathway. Akt inhibits glycogen synthase kinase 3β (GSK-3β). **e**) LiCl inhibits IFN-γ mediated GSK-3β signalling. **f**) GSK-3β phosphorylates β-catenin, which causes its degradation. LiCl-mediated inhibition of GSK-3β via various signalling pathways (a, b, e) inhibits β-catenin degradation. β-catenin nuclear translocation leads to transcription of cyclin D1 (cell cycle regulator). **g**) LiCl-mediated GSK-3β inhibition impedes Signal transducer and activator of transcription (STAT) factor nuclear translocation that downregulates transcription of Indoleamine 2,3-dioxygenase (IDO1). Inhibition of IDO1 prevents tryptophan metabolism, which inhibits the kynurenine pathway and hence reduces pro-inflammatory cytokine activity. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

reduce the phosphorylation and the related excitotoxicity. Li may reduce the availability of PKC for phosphorylation by reducing its translocation [106]. Glutamate-induced excitotoxicity has also been observed in other neurodegenerative diseases, such as AD, ALS, PD, HD, stroke, brain trauma, and spinal cord injury [107].

NMDA receptor-mediated Ca^{2+} influx, and neuronal nitric oxide synthase (nNOS) activation can differentially regulate the Extracellular signal-Regulated Kinase (ERK) signal transduction pathway in neuronal cells [108]. Jaffari *et al.* showed the neuroprotective effect of LiCl against glutamate excitotoxicity *via* phospho-ERK/NMDA receptor/NO signalling in the PTZ-induced clonic seizure model [93]. The study showed that the effect of acute Li (10-60 mg/Kg, therapeutic range) pretreatment reduced the seizure threshold resulting in proconvulsant effects in the PTZ model, whereas chronic pre-treatment with similar doses produced an anti-convulsant effect in NMRI mice. Therefore, it appears that Li requires chronic pre-treatment for maximal neuroprotective effects in animal models [93, 103]. In the Middle Cerebral Artery Occlusion (MCAO) model, the hypoxia-induced ischemic injury resulted in significant glutamate efflux and higher pH favouring NMDA receptor activation. Subcutaneous pretreatment of LiCl (1.5 - 3 mEq/kg) for 16 days reduced brain damage up to 56% in Wistar rats [103]. However, the incomplete protection observed shows the involvement of other mechanisms which were not affected by Li treatment.

Evidence shows that Li prevents NMDA-induced toxicity through mechanisms such as altering NMDAR subunit phosphorylation, enhancing glutamate reuptake, decreasing NMDAR gene expression, and also indirectly enhancing the neurotrophic factors such as BDNF [105]. This can be proved since the presence of a BDNF neutralizing antibody reversed the protective effect of Li over glutamate-induced excitotoxicity in rat cortical neurons [102].

4.2. NO/cGMP Pathway

Nitric Oxide (NO) is a key endogenous signalling molecule that exerts its effects by influencing different signalling pathways and post-translational modifications of different proteins. NO plays an essential role in various physiological activities in the brain, such as neuronal signalling, synaptic

plasticity, and excitability, apart from its functions in immune function and vasodilation, *etc.* Hence, aberrant nitric oxide signalling is implicated in various neurological and neurodegenerative diseases. NMDA overactivation followed by Ca^{2+} accumulation induces neuronal nitric oxide synthase (nNOS) activation, which further induces cGMP production that leads to nitric acid release [109].

cGMP is shown to modulate seizure susceptibility in several animal models. Li is reported to regulate the NO/cGMP transmission, and in certain conditions such as seizures, Li inhibits this pathway resulting in anti-convulsant action. A single dose of Li (25 mg/kg, i.p.) increased the seizure threshold in the PTZ model of clonic seizures in NMRI mice *via* the NO-cGMP pathway [88]. The effect of Li was potentiated with nNOS inhibitor, 7-nitroindole, and cGMP inhibitor methylene blue, and reversed by NO precursor L-arginine; however, the inducible NOS (iNOS) inhibitor did not exert any influence. A similar neuroprotective effect of Li was observed in other seizure models, such as the maximal electric shock and PTZ-induced seizure models [93, 110]. Honar *et al.* showed the anti-convulsive effect of LiCl on morphine's biphasic modulation of susceptibility to PTZ-induced clonic seizure in mice. In this study, LiCl (0.05 mg/kg) inhibited the anti-convulsant (morphine 1 mg/kg) and proconvulsant (morphine 30 mg/kg) effect of morphine when administered along with a noneffective low dose of naloxone (0.1 mg/kg) [111]. The study suggested that LiCl inhibited the opioid signal transduction rather than inhibiting the opioid receptors.

In another study, Rahimi *et al.* showed better anti-seizure activity of LiCl compared with other alkali metal, rubidium chloride, in PTZ (0.5%, 1 mL/min) induced seizure model in mice [112]. The study showed the anti-convulsant effects of LiCl (doses higher than 5 mg/kg) after 30 min on PTZ-induced seizures. Also, when LiCl (1 mg/ml, i.p.) was administered with L-NAME (NOS inhibitor) and MK-801 (NMDA receptor antagonist), it potentiated the anti-seizure activity. Whereas L-arginine, a NOS precursor administration, decreased the seizure threshold of LiCl. The study demonstrated that NMDA/nitrergic pathways mediated the anti-seizure effect of LiCl in PTZ induced seizure model. Similarly, acute low dose Li (3 mg/kg) prevented the proconvulsant potential of social isolation-induced stress by inhibiting the nitrergic signalling in the PTZ model of clonic seizures in mice [113].

4.3. Neurotransmitters

Li treats bipolar disorders by modulating neurotransmission, where the long-term Li treatment decreases excitatory neurotransmission and increases GABAergic transmission [114]. Recently, a dose-dependent effect (10-127 mg/kg, i.p.) of Li on brain EEG rhythms has been observed in the pilocarpine model of seizures [18]. Interestingly, LiCl at a lower dose (10 mg/kg) increased the basal gamma and theta power in the EEG spectrogram, correlating with decreased seizure severity and susceptibility. At the same time, a higher dose (40 mg/kg) produced the opposite effect. The electrophysiological investigation of rats showed an imbalance between excitatory and inhibitory neuronal networks, which resulted in abnormal neural activity. The study explicitly demonstrated that with increasing doses of Li, the dose of pilocarpine required for seizure induction is reduced [18].

Acute LiCl (30 mg/kg, i.p.) treatment increased the seizure threshold in the PTZ seizure test in NMRI mice, which was reversed by clonidine, an α2-adrenoceptor agonist. The decreased seizure threshold upon clonidine administration demonstrates the possible involvement of the α2-adrenergic system in the anti-convulsant action of Li [115].

4.4. Modulation of the GSK-3β Pathway

GSK-3β regulates various cellular processes such as cellular survival, inflammation, Long-Term Potentiation (LTP), and synaptic reorganization. Emerging studies have highlighted the role of the GSK-3β pathway in neuronal excitability and neuropathology of epilepsy [116, 117]. As GSK-3β regulates various ion channel functions in controlling excitability, it is a vital target relevant to epilepsy [116]. In drug-resistant epileptic patients, elevated mRNA and protein levels of GSK-3β were reported [118]. Interestingly, inhibition of GSK-3β by 6-bromoindirubin-3'-oxime (Bio-acetoxime) in the *in vivo* models such as PTZ-zebrafish, pilocarpine, and 6-Hz kindling seizures showed anti-convulsant activity [119]. Several *in vitro* studies also demonstrate the protective effect of Li over seizure-induced excitotoxicity and hippocampal neuronal death by inhibiting GSK-3β [120]. It is shown that GSK-3β inhibition reduced phosphorylation of c-Jun, which augmented c-Jun DNA binding activity and therefore increased the expression of neuroprotective genes [103]. Along similar lines, LiCl treatment reduced neuronal death and cognitive impairment and improved the excitotoxicity index (glutamate × glycine/GABA) in the intracerebral haemorrhage model of rats. LiCl (60 mg/kg, i.p., twice daily for 14 days) suppressed glutamate excitotoxicity by inhibiting downstream collapsin response mediator protein-2 (CRMP-2)/NMDA receptor subunit (NR2B) signalling. On the other hand, it inhibited GSK-3β and stabilized β catenin, altogether inhibiting apoptosis [17].

GSK-3β is considered to have a proapoptotic role, and thus its inhibition confers cytoprotection [121]. A study done by Yazlovitskaya showed that LiCl (40 mg/kg or 80 mg/kg, i.p.) treatment protected the hippocampal neurons from irradiation-induced apoptosis by inhibiting the GSK-3β pathway and synthesis of Bax protein. Interestingly, five days of pretreatment with LiCl protected the neuronal cells, but no change in cell viability was observed when HT-22 cells were pre-treated just 24 h before irradiation [122].

Lithium is also reported to be an activator of Wnt/β-catenin signaling, which influences cell survival decisions in the brain [123]. The Wnt pathway is disrupted in several diseases, including epilepsy, affecting seizure-induced neuronal death and neurogenesis [124]. DKK-1, a known physiological antagonist of the Wnt pathway, is involved in seizure-induced neuronal damage. It activates GSK-3β and other proteins that mediate the proteasomal degradation of β-catenin, and β-catenin is essential for neuronal survival and homeostasis. Li inhibits GSK-3β and rescues the Wnt/ β-catenin pathway, involved in seizure-induced neuronal damage, by blocking the downstream of Dkk-1 [125, 126]. Pretreatment with chronic Li (1 mEq/kg, i.p.) alleviated the neuronal damage without influencing the seizure characteristics in the kainite model of seizures [126].

Furthermore, Li treatment showed improvement in symptoms associated with the rare chromosomal disorder (Ring

chromosome 20-syndrome) characterised by refractory epilepsy with cognitive impairment and behavioural aggressiveness [96]. The silencing of KCNQ2, a gene encoding for potassium channels in neurons, is proposed to be involved in the pathophysiology of this disease. Both GSK3β and IMPase are reported to regulate the function of KCNQ2 channels. Therefore, it is possible that Li inhibited the phosphorylation of KCNQ2 channels by inhibiting the GSK3β and IMPase. Thus, Li could maintain the K+ channel open, causing neuronal hyperpolarization, and showed an anti-convulsant effect with reduced aggressiveness, irritability, and impulsivity [127].

Above all, Engel *et al.* showed that either an increase or decrease of GSK-3β aggravated seizure severity and hippocampal damage in C57BL6 mice, demonstrating narrow tolerance for manipulating this pathway [85]. Along these lines, further studies clarifying the influence of Li over GSK-3 in the context of seizures and epilepsy are warranted.

DISCUSSION AND CONCLUSION

Altogether, the above experimental and clinical evidence strongly states that the association of Li with seizures is most likely dose-dependent. Li at higher doses (>1.2 mmol/l) has clearly shown a decrease in the seizure threshold and led to seizures. However, in specific contexts such as with cholinomimetics, even at lower doses, Li potentiated the seizures; data was limited to the experimental studies. Existing evidence indicates that the reduction in seizure threshold could be majorly through various mechanisms such as increasing cholinergic activity, inhibiting phosphoinositide metabolism and GSK-3β signalling, and inducing peripheral inflammation.

Although few primitive clinical reports and a lithium-pilocarpine animal model point out that Li can be proconvulsive, a plethora of evidence highlights its neuroprotective effects in patients as well as in animal studies with chronic treatment. Studies involving chronic low dose treatment showed anti-convulsant and neuroprotective effects by inhibiting the NMDA-mediated excitotoxicity and modulating GSK-3β signalling. Despite this inference, numerous speculations need to be addressed before considering Li in epileptic patients.

Electrophysiological studies in human iPSCs revealed a concentration-dependent marked increase in neuronal firing and excitatory glutamatergic drive in case of acute treatment, whereas a decrease was observed with chronic treatment. Therefore, acute Li treatment might pose a risk to patients with epilepsy. Besides, as previously discussed, serum Li concentrations do not necessarily reflect brain Li concentrations in every patient, which needs discretion.

Altogether, there are no recent studies to evaluate its safety in the epileptic population, which can provide a realistic picture of the safety of Li in the presence of AEDs, other co-morbidities, long-term treatment, *etc.* Of note, the acute and *in vitro* Li treatment studies that demonstrated the simple mechanistic interpretations based on the transient biochemical effects are irrelevant, and therefore, translating these results for clinical value is inappropriate. So, observational retrospective studies are needed to assess the impact of Li on the quality of life of epileptic patients.

With the advent of various high throughput and advanced technologies such as RNAseq and bioinformatic tools, the intricate molecular crosstalk through which Li mediates its effects in epilepsy should be re-examined. Still, it would be challenging since the molecular effects of Li are highly heterogeneous, and only a fraction might be responsible for its effects on seizures, which further need to be thoroughly explored.

LIST OF ABBREVIATIONS

Akt aka PKB	=	Serine/Threonine-protein Kinase (Protein Kinase B)
BDNF	=	Brain-derived Neurotrophic Factor
DAG	=	Diacylglycerol
GluA1	=	Glutamate Ionotropic Receptor AMPA Type Subunit 1 (GluA1)
IDO1	=	Indoleamine 2,3-dioxygenase
IMPase	=	Inositol Monophosphatase
IP2	=	Inositol 4,5 Bisphosphate
IP3	=	Inositol 1,4,5 Triphosphate
Li	=	Lithium
LiCl	=	Lithium Chloride
NO	=	Nitric Oxide
NOS	=	Nitric Oxide Synthase
NR2B	=	NMDA Receptor 2B
PI	=	Phosphatidylinositol 5-phosphate
PI3K	=	Phosphatidylinositol 3'-kinase
PIP2	=	Phosphatidylinositol 4,5-bisphoshate
PIP2	=	Phosphatidylinositol 4,5-bisphosphate
PKC	=	Protein Kinase C
PLC	=	Phospholipase C
STAT	=	Signal Transducer and Activator of Transcription
TrkB	=	Tropomyosin Receptor Kinase B

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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HIGHLIGHTS

- In most animal studies, acute lithium (Li) treatment favoured dose-dependent proconvulsant action through multiple mechanisms such as increasing neuronal excitability, enhancing cholinergic pathways, inhibiting phosphoinositide signalling, and promoting peripheral inflammation.
- Chronic Li treatment produced anti-convulsant action through neuroprotective mechanisms such as inhibiting NMDA/NO signalling and GSK-3β signalling.
- PI signalling and GSK-3β are the prime targets of Li through which it mediates a broad range of actions
- GSK-3β inhibition by Li can be a double-edged sword in the context of seizures and epilepsy, warranting further studies.
- Numerous gaps exist in the available literature concerning the role of Li in epilepsy, hence demanding more preclinical and clinical studies to examine its effects critically.

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