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Invited Mini Review

Lithium: the protective cation singled out by Alzheimer's disease

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Lithium is a mood stabilizer that is most prescribed in psychiatry for managing mental disorders. Many findings indicate that lithium is also neuroprotective in various neurodegenerative diseases. In particular, lithium has been of great interest as an affordable but still effective treatment for Alzheimer's disease (AD), due to its diverse neuroprotective actions and mechanistic overlap with key AD pathways, such as Aβ production and tau modification. While the multifaceted activities may result from lithium's inhibitory action on two key enzymes, glycogen synthase kinase-3 beta (GSK-3β) and inositol monophosphatase (IMPase), recent findings suggest that selective lithium depletion in neurons mediated by amyloid deposits may be a key pathological trigger in AD and supplementation with lithium orotate, a lithium salt with reduced amyloid binding, may even reverse brain damage and prevent cognitive decline. In this study, we review the neuroprotective properties of lithium, its known mechanisms of action, and discuss its therapeutic potential in AD, a topic that has been debated for decades. [BMB Reports 2026; 59(10): 456-465]

INTRODUCTION

Lithium is the lightest and least dense alkali metal, with an atomic number of 3. It is highly reactive and readily reduced to become a cationic ion, which easily dissolves in water and is commonly found in various earth deposits (1). Lithium is broadly detected in numerous biological organisms, including protozoa, animals, and plants, at concentrations ranging from 0.1 mg to several g kg-1 (2). Although it is largely unknown why and how lithium accumulates in various species and whether it affects their specific physiological functions, the causal relationship between lithium levels and human health has been reported. Levels lower than 0.6 mM of lithium in serum are linked to mental disorders, and levels higher than 1.5 mM are usually toxic, inducing dysfunctions of various organs such as the kidney, thyroid, and reproductive system (2).

Lithium's antimanic effects were first reported in 1949, and it was approved by the U.S. Food and Drug Administration (FDA) for the treatment of acute mania and maintenance therapy of manic patients in the 1970s (3, 4). Since then, lithium has become one of the most prescribed drugs for treating various mental disorders, including mania, depression, bipolar disorder, and schizophrenia. However, long-term treatment of lithium is linked to adverse effects and complications, such as memory impairment and kidney dysfunction. In 1979, it was first reported that lithium has a positive effect on cognition; Dementia patients with agitated depression who received lithium treatment experienced a dramatic improvement in their cognition (5). In the 1990s, it was reported that healthy individuals taking lithium improved their cognitive performance (6). In 1993, lithium's neuroprotective effects in Alzheimer's disease (AD) started to draw a lot of attention when dementia patients treated with lithium salts exhibited lower levels of amyloid precursor protein than those receiving other psychiatric medications, such as antidepressants, antipsychotics, and tranquilizers (7). Interest in lithium's potential for AD therapeutics increased after it was reported that a specific subgroup of BD patients taking lithium as their sole medication could restore normal clinical profiles and cognitive function (8). Over the past 30 years, considerable evidence has demonstrated the neuroprotective effect of lithium in AD, and its molecular and cellular mechanisms of action have been extensively explored (9, 10).

Lithium inhibits glycogen synthase kinase-3β (GSK-3β) and inositol monophosphatase (IMP), and the inhibition of these two enzymes plays a pivotal role in its therapeutic effects and modulation of other intracellular pathways (11, 12). This leads to downstream effects on signaling pathways implicated in neuroprotection. Recently, the Yankner group reported that amyloid β (Aβ) plaques sequester lithium, reducing its bioavailability (13). They reported that a reduction in lithium levels increases Aβ deposition and phospho-tau accumulation, leading to pro-inflammatory microglial activation, loss of

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synapses, axons, and myelin, and accelerated cognitive decline. Replacement therapy with lithium orotate, which has reduced amyloid binding, prevents these pathological changes and cognitive decline in AD mouse models and aging wild-type mice. In this review, we provide an overview of the protective roles of lithium in AD, explore current hypotheses regarding its mechanisms of action, and discuss its potential as a therapeutic approach for the prevention and treatment of AD.

Lithium's neuroprotective properties

Lithium has been shown to have various neuroprotective effects, primarily in experimental models (14). Lithium therapy has shown neuroprotective effects in various AD mouse and rat models by inhibiting GSK-3β activity. It reduces Aβ deposition and tau phosphorylation, regulates autophagy, oxidative stress, cholinergic signaling, and glucose metabolism, enhances neurogenesis and synaptic plasticity, maintains mitochondrial homeostasis, and restores memory and improves cognitive function (15-24). Long-term lithium use in AD patients is associated with an increase in gray matter volume in the cerebrum, improved tissue viability, and a reduced incidence of dementia (25, 26). Lithium's neuroprotective properties are thought to be attributed to the inhibition of GSK-3β and IMPase and the regulation of subsequent downstream pathways (10).

Lithium's action on GSK-3β and its effects on AD pathology

GSK is a Ser/Thr protein kinase involved in the regulation of many key cellular processes (27). There are two GSK isoforms: GSK-3α and GSK-3β (28). While both isoforms are ubiquitously expressed and constitutively active, GSK-3β is more abundant in the brain, and its expression increases with age (29). GSK-3β expression and activity are increased in the brain of AD patients, and the abnormal increase contributes to the pathogenesis of AD (30). GSK-3β is pharmacologically inhibited by lithium, which suppresses its kinase activity by directly competing with magnesium ions and indirectly modulating the phosphatidylinositol 3-kinase (PI3K)/serine/threonine kinase Akt-1 signaling pathway that promotes the phosphorylation of GSK-3β (11, 31). Lithium also inhibits GSK-3 transcription, thereby reducing its expression (32). The GSK-3β inhibition leads to the nuclear accumulation of β-catenin, which interacts with the TCF/LEF family of transcription factors to regulate the transcription of target genes (33). This ultimately reduces Aβ deposition and phospho-tau accumulation, promoting neuronal survival and neurogenesis (34-37). By inhibiting GSK-3β, lithium activates the nuclear factor erythroid 2-related factor (NRF2)/antioxidant response element (ARE) pathway, likely reducing oxidative stress (16, 38, 39). It also inhibits nuclear factor kappa-B (NF-κB) and signal transducer and activator of transcription 3 (STAT-3), attenuating neuroinflammation (40-42). These effects help the nervous system maintain its structure and function and are targeted in therapeutic strategies for AD treatment.

Lithium's action on IMPase and its effects on autophagy

Lithium decreases IP3 signaling, thereby inducing autophagy through an mTOR-independent pathway (43). IMPase is a phosphodiesterase that removes phosphate of inositol monophosphate to generate free myo-inositol, contributing to phosphatidylinositol signaling (44, 45). Lithium inhibits IMPase and inositol polyphosphate-1-phosphatase (IPPase), thereby depleting free inositol, a precursor of inositol 1,4,5-trisphosphate (IP3), and consequently reducing IP3 production (46-48). The induced autophagy cleans up aggregation-prone proteins, such as Aβ and phospho-tau, offering therapeutic benefits for neurocognitive and psychiatric disorders (49, 50). On the other hand, inhibiting GSK-3β may downregulate autophagy by activating the mTOR pathway and reducing the activity of ULK1 (Unc-51-like autophagy activating kinase 1), which initiates formation of autophagosomes (51, 52). Therefore, treatment with both lithium and rapamycin, which suppresses mTOR, has been proposed to enhance the clearance of neurotoxic proteins (45). Inhibition of both IMPase and GSK-3β inherently drives autophagy in opposite directions, setting up a tug-of-war that balances autophagy at different levels in different cell types and stages of AD. At relatively low lithium concentrations, IMP inhibition (Ki $\approx$ 0.8 mM) usually predominates, thereby activating autophagy (43). However, inhibition of GSK-3β becomes stronger at higher concentrations (Ki $\approx$ 2 mM), suppressing autophagy (53). Neurons with high autophagy activity respond efficiently to IMP inhibition to induce autophagy, whereas astrocytes with low autophagy activity activate the PI3K/Akt/mTOR pathway to promote survival and proliferation rather than suppress autophagy. Microglia are inflammatory cells in the brain and likely respond to lithium in the context of inflammatory signaling, which profoundly influences autophagy presumably through both the GSK-3β and IMP pathways (13, 54, 55). Microglial autophagy has protective effects in early AD. However, in late AD, lysosomal function is often impaired; thus, autophagosomes accumulate, and further autophagosome formation is no longer protective in pathological conditions.

Lithium deficiency in AD

Lithium enters cells through voltage-gated Na^+ channels, which are opened by synaptic activity, and neurons that are frequently excited accumulate more lithium than inactive neurons (56). Active neurons increase the volume of neural structures in the prefrontal cortex, hippocampus, and amygdala (57, 58). Dietary intake of lithium is required for maintenance of lithium homeostasis in the brain, but it is challenging to properly perform lithium therapy due to its narrow window of dosing to avoid nephrotoxic effects (59, 60). It has been speculated that lithium toxicity may be driven by the rapid ionization of lithium salts, such as lithium chloride or lithium carbonate, widely used in studies (Table 1).

A recent study demonstrates that lithium deficiency in the brain plays a significant role in the progression of early

Table 1. Clinical trials using lithium for MCI or AD individuals

Formulation	Daily dose	Serum level	Duration	Treatment (N, age mean ± SD)	Placebo (N, age mean ± SD)	Stage (MCI/AD)	Medical history	Outcomes and readouts	Key limitations	Study design	Remarks	Ref.
Lithium carbonate	150 or 300 mg	0.17 ± 0.13 mmol/L (at the end of the trial)	2 years	N = 41 72.93 ± 8.77	N = 39 71.22 ± 6.47	MCI (Petersen criteria)	No statistical differences in the medication counts	- Cognitive function (PACC, BVMT-R, CVLT-II) - Neuroimaging (Cortex and hippocampus volume) - Biomarker (BDNF) All insignificant results (CVLT-II 0.01 < P< 0.05, the the rest P > 0.05)	- Performed during the COVID-19 - Included amnestic MCI with Aβ- (PET imaging)	- Randomized - DB - Placebo-controlled - Parallel-group - Single-center	Threshold P-value was 0.01	(87)
	300 μg		52 weeks	total N = 46, 79.4 ± 5.4		Mild to moderate AD (DSM-V criteria CDR > 1 or 2)		Cognitive function (ADAS-cog, MMSE) All insignificant results		- Randomized - DB - Placebo-controlled	Unpublished	(86)
	150-600 mg	0.2-0.6 mmol/L	12 weeks	N = 37 75.6 ± 8.4	N = 35 74.3 ± 7.2	Probable AD (NIA criteria; MMSE score 5-26; NPI domain score for agitation/aggression ≥ 4)	The detailed study design is described in (89)	BDNF concentration, total NPI, agitation/aggression, psychosis, and cognitive function (MMSE) All insignificant results (P > 0.05)	- Small sample size - Short duration of treatment - No Aβ PET imaging	- Randomized - DB - Placebo-controlled - Parallel-group - Multicenter		(88)
				N = 38 75.6 ± 8.3	N = 39 74.3 ± 6.9		Cholinesterase inhibitors, memantine, antidepressants, antipsychotics, or Lorazepam	- NPI agitation/aggression (P = 0.53) - Treatment response (30% reduction in NPI score for agitation/aggression plus psychosis and a CGI score of much or very much improved, P = 0.26) - CGI global change (P < 0.001) - NPI delusions and irritability/lability (P < 0.05) - High YMRS patients (P = 0.01)		- Randomized - DB - Placebo-controlled - Parallel-group - Multicenter - Investigator-initiated		(89)
	150, 300, 450, or 600 mg	0.25-0.5 mmol/L	2 (DB) + 1 (SB) years	N = 31 71.2 ± 5.4	N = 30 74.4 ± 6.1	Amnestic MCI (according to Mayo Clinic criteria)	No statistical differences in the frequency of systemic hypertension, osteoarthritis, dyslipidemia, hypothyroidism, diabetes mellitus, and minor depression	- Cognitive (ADAS-cog; P < 0.05) and functional (CDR-SB; P < 0.05) parameters - Neuropsychological test (WAIS-III) scores with emphasis on memory, attention and executive functions; Delayed recall (P < 0.001), Figure recall (P = 0.02), Trail making test-A (P < 0.01); Other attention tests such as letters and numbers, and trail making test-B (insignificant) - Aβ peptide concentrations in CSF overall (P > 0.05 after 12 months, P = 0.003 after 36 months) and from high Aβ group (P = 0.04 after 36 months); total tau and p-tau 181 (P > 0.05) - Conversion from MCI to dementia (P = 0.06)	- Small sample size - No Aβ PET imaging	- Randomized - DB - Placebo-controlled - Parallel-group - Single center - Intervention trial followed by a SB extension phase for an additional 24 months		(85)
			1 year	N = 23 70.9 ± 5.3	N = 22 74.2 ± 6.5		The approval by general practitioner required for enrollment of individuals with comorbidities	- P-tau 181 concentration (P = 0.02) - P-tau 181 in those who remained stable (P = 0.006) or progressed to AD (P = 0.90) - Total tau or Aβ42 concentration (P > 0.05) - Cognitive and functional decline in those who progressed to AD (placebo group P = 0.03, lithium group P = 0.3)		- Randomized - DB - Placebo-controlled - Parallel-group - Single center		(83)
	100 mg	0.3-0.8 mmol/L	1 year	N = 22 80.9 ± 7.9 (14 ceased lithium)	1:2 matching from same research group	Probable or possible AD (NINCDS-ADRDA criteria, MMSE score 12-24)	Individuals treated with antidementia medication, not excluded	- Lithium side effects scale difference between those who completed and those who did not (P > 0.05) - Cognition (MMSE over 1 year, P > 0.05) - No correlation between mean lithium concentration achieved and cognition (MMSE) or function (Bayer) scale	- Small sample size - High attrition rate - No Aβ PET imaging	- Open label - Pragmatic clinical trial		(90)

Table 1. Continued

Formulation	Daily dose	Serum level	Duration	Treatment (N, age mean ± SD)	Placebo (N, age mean ± SD)	Stage (MCI/AD)	Medical history	Outcomes and readouts	Key limitations	Study design	Remarks	Ref.
Lithium carbonate or Lithium gluconate	300 μg	Unknown	15 months	N = 58 77 ± 0.97	N = 55 78.0 ± 0.76	AD diagnosis (MMSE score of 9-21 for ≤ 4 years of education, and 12-24 for > 4 years)	No statistical differences in the use of acetylcholinesterase inhibitors, N-Methyl-D-aspartic acid inhibitors, angiotensin converter enzyme inhibitor, and hypoglycemic agents	Cognitive function (MMSE score, P< 0.001)	- Small sample size - MMSE is the only outcome variable - No Aβ PET imaging	- Randomized - DB - Placebo-controlled - Parallel-group		(84)
Lithium sulphate	84-336 mg	0.5-0.8 mmol/L	10 weeks	N = 13 69.4 ± 8.5	N = 14 71.0 ± 9.0	Mild AD (NINCDS-ADRDA and DSM-IV criteria)	Individuals with concomitant use of valproic acid, memantine, neuroleptics, coumarin anticoagulants, or nonsteroidal anti-inflammatory drugs, excluded	Negative correlation - Lithium concentration in serum and GDNF concentration in CSF (r = −0.585, P = 0.036) - Lithium concentration in serum and differences in GDNF concentration in CSF (r = −0.755, P = 0.003) - ADAS-cog (P < 0.05) -GDNF in serum (P = 0.755) or in CSF (P = 0.557) between lithium and placebo groups - MMSE (P = 0.67, corrected z-scores P = 0.1)	- Small sample size - Short duration of treatment - No Aβ PET imaging	- Randomized - SB - Placebo-controlled - Parallel-group - Multicenter	Same patient groups as (93)	(91)
				N = 33 68.2 ± 7.2	N = 38 68.9 ± 8.3	Mild AD (NINCDS-ADRDA criteria and DSM-IV-TR, MMSE score 21-26)		- GSK-3 activity; p-tau 181, p-tau 231, total tau, and Aβ42 level - ADAS-cog, MMSE, and NPI scores All insignificant results				(92)
				N = 13 69.4 ± 8.5	N = 14 71.0 ± 9.0	Mild AD (NINCDS-ADRDA criteria and DSM-IV criteria)		- Significant interaction of time and treatment in BDNF concentrations in serum (P = 0.035) and in ADAS-cog (P = 0.015) - BDNF concentration in serum compared to healthy controls (P = 0.7242) Negative correlation - Lithium concentration in serum and changes in ADAS-cog (r = −0.641, P = 0.025) No correlation - Lithium concentration in serum and BDNF level changes (r = 0.175, P = 0.568) - ADAS-cog and BDNF changes (r = −0.187, P = 0.349)			Same patient groups as (91)	(93)

AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; BDNF, Brain-Derived Neurotrophic Factor; BVMT-R, Brief Visuospatial Memory Test-Revised; CSF, Cerebrospinal Fluid; CDR-SB, Clinical Dementia Rating–Sum of Boxes; CGI, Clinical Global Impressions; CVLT-II, California Verbal Learning Test-II; DB, Double-Blind; DSM, Diagnostic and Statistical Manual of Mental Disorders; GDNF, Glial Cell Line-Derived Neurotrophic Factor; MCI, Mild Cognitive Impairment; MMSE, Mini-Mental State Examination; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NPI, Neuropsychiatric Inventory; PACC, Preclinical Alzheimer Cognitive Composite; PET, Positron Emission Tomography; SB, Single-Blind; YMRS, Young Mania Rating Scale; WAIS-III, Wechsler Adult Intelligence Scale-III.

pathogenesis of AD (Fig. 1) (13). Out of 27 metals analyzed, only lithium is significantly reduced in the brains of individuals with AD or mild cognitive impairment (MCI) and the specific depletion results from sequestration by Aβ plaques. Moreover, lithium does not promote plaque formation. These are intriguing findings because other metal ions, such as copper (Cu), zinc (Zn), and iron (Fe), are also concentrated in Aβ plaques and promote Aβ aggregation (61). However, none of them show the local depletion near Aβ plaques as lithium does. The concentrations of Cu and Zn are not simply increased or decreased in AD brains. Rather, they are redistributed throughout brain regions and within and outside neurons (62). It has been reported that intracellular bioavailable Cu and Zn are typically reduced, accompanied by dysfunctional buffering systems, whereas the extracellular and plasma levels are increased or variable in regions such as the hippocampus and cerebral cortex (63-65). Unlike Cu and Zn, Fe levels are usually elevated in vulnerable regions, such as the hippocampus and cerebral cortex, and the accumulation of this highly redox-active metal induces oxidative stress, which broadly impairs

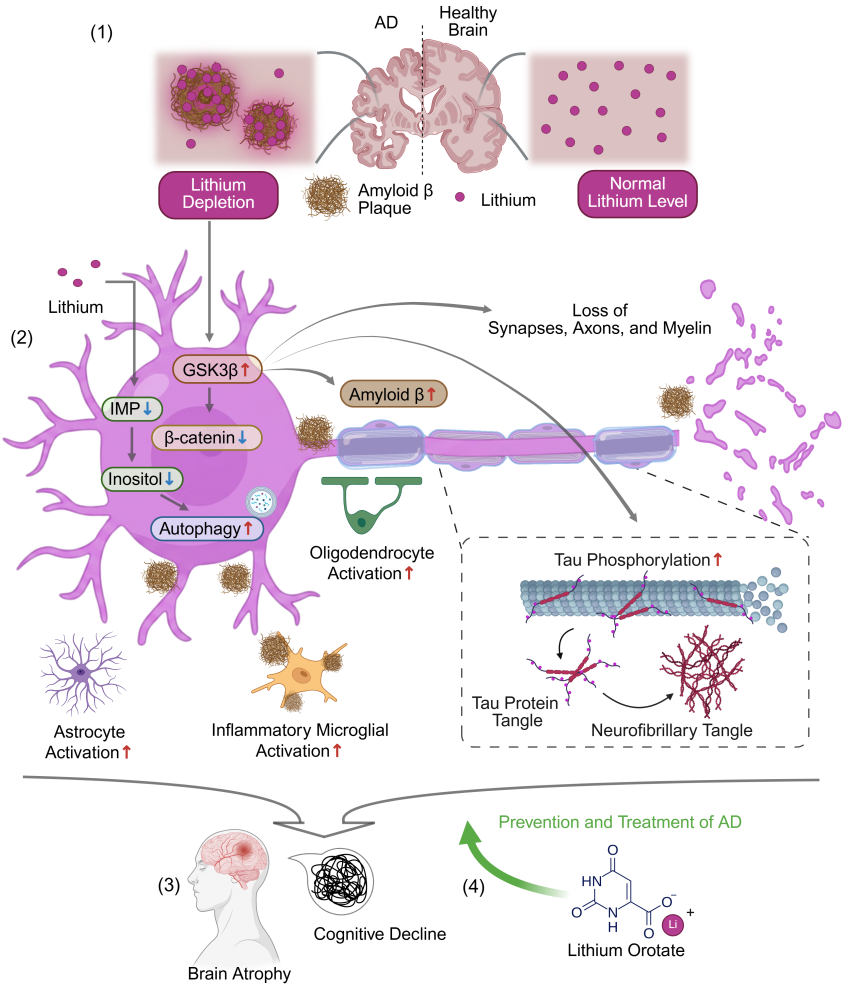

Fig. 1. Lithium depletion by amyloide β (Aβ) plaques in Alzheimer's disease. (1) In the Alzheimer's disease (AD) brain, lithium (Li) is sequestered by Aβ plaques, resulting in Li depletion in nearby regions. (2) The Li depletion leads to increased Aβ deposition and phospho-tau accumulation. In Li-deficient neurons and glial cells, GSK3β expression and activity are markedly increased. As a result, the nuclear accumulation of β-catenin, a target of GSK3β, is reduced, and the weakened β-catenin pathway results in the breakdown of synapse assembly and axonal myelin. Microglia, oligodendrocytes, and astrocytes become reactive in the resulting pathological situations by releasing various pro-inflammatory cytokines and immune-activating chemokines. Lithium inhibits inositol monophosphatase (IMP), which generates free inositol that inhibits autophagy in neurodegenerative models. Therefore, Li depletion may perturb inositol levels, thereby impairing autophagy and promoting Aβ accumulation. (3) The molecular and cellular consequences of Li depletion ultimately contribute to brain atrophy and cognitive decline. (4) Lithium orotate, a lithium salt with reduced amyloid binding, has been shown to generally prevent Alzheimer's disease symptoms and even reverse declines in learning and memory by evading sequestration by Aβ plaques and increasing Li levels in the brain. Created with BioRender.com. GSK3β, glycogen synthase kinase 3β; IMP, inositol monophosphatase.

brain function and accelerates AD pathology (66-68).

Lithium depletion in the brain promotes Aβ deposition, tau phosphorylation, neuroinflammation, synaptic and myelin loss, and cognitive decline, and many of these pathologic events are mediated in part by GSK-3β activation (13). It also induces AD-like gene expression changes in various brain cells, including microglia, astrocytes, and oligodendrocytes. Interestingly, dietary supplementation with lithium orotate (LiO), an organic lithium salt with low ionization capacity and reduced amyloid-binding activity, prevents those pathological changes in AD or aging mice. It also restores microglia's ability to clear Aβ and reverses the decline in learning and memory. Despite the lack of human clinical data, this study suggests that disruption of lithium homeostasis may be one of the early events in AD development, and that lithium supplementation with amyloid-evading LiO may offer a potential preventive or therapeutic opportunities for AD.

Why only lithium selectively depleted near Aβ plaques?

Although it is unknown why only lithium is significantly depleted around Aβ plaques, while many other critical ions in the brain, including Cu^{2+}, Zn^{2+}, and Fe^{2+}, are not, several features of lithium may help answer the question of why lithium becomes selectively sequestered by Aβ plaques, and its bioavailability is decreased (69).

Lithium is the smallest alkali metal ion and highly mobile. It has a very high charge density, readily dissolves in water and rapidly diffuses through the extracellular space, and easily enters narrow molecular structures (70). Because Aβ plaques consist of dense aggregates of β-sheet, which contain many negatively polarized oxygen-containing groups, Li^+ may diffuse into these microstructures and become retained more readily than other larger alkali metal ions abundant in the brain, such as Na^+ or K^+ (71, 72).

In Aβ plaques, ions may be abnormally trapped in certain microenvironments because Aβ fibrils contain carbonyl oxygens, carboxyl groups, polar peptide backbones, and nanospaces filled with water, in which cations can be locally coordinated with those chemical structures (73-75). Lithium has high hydration energy and a small ionic radius, so it may accumulate in confined hydrated pockets within plaques.

Unlike other abundant cations such as Cu^{2+}, Zn^{2+}, and Fe^{2+}, lithium does not strongly bind to proteins in the normal brain. There are no storage proteins for lithium (e.g., copper storage proteins for Cu^+, ferritin for Fe^{3+}) or buffering systems (e.g., metallothioneins for Cu^{2+} and Zn^{2+}; calbindin and calreticulin for Ca^{2+}) (76-80). If Aβ plaques act as an ionic sink, free lithium may be selectively trapped, given minimal intracellular buffering and the extremely low extracellular concentration.

It is also noteworthy that lithium can form organolithium compounds with carbon–lithium bonds, which tend to aggregate into clusters (81). Also, radical anions of various organic compounds, including alkyl, aryl, and polycyclic aromatic compounds, can form lithium salts and anions of those organic compounds may form as a result of oxidative stress induced by Aβ deposition.

Why is lithium orotate (LiO) more effective?

Lithium is an alkali metal and naturally forms salts with various anions (14). For the last several decades, lithium carbonate (Li_2CO_3), lithium chloride (LiCl), and lithium sulfate (Li_2SO_4) have been primarily used in experimental AD models, and these lithium salts have high ionization capacity and conductivity; thus, they are often administered at high doses to exert neuroprotective effects (Table 1). Due to the side effects and toxicity of lithium salts, non-toxic lithium formulations have been explored in lithium therapeutics for AD (58, 82). Although some small clinical trials indicate that lower concentrations of lithium carbonate or lithium gluconate reduce cognitive decline (83-85), a random-effects model meta-analysis incorporating currently available data reveals no beneficial effects of carbonate, gluconate and sulfate forms of lithium salts on cognition (86). Almost all of the previous clinical trials neither confirm Aβ plaque formation by PET imaging nor measure other AD biomarkers, such as Aβ and tau levels in cerebrospinal fluid (CSF) (Table 1) (87-93). Instead, they rely on cognitive and functional test scores as their primary outcomes and have many mismatches between biomarker readouts and test results. Therefore, it is unclear whether participants in the clinical trials are actual AD patients. In many cases, participants are on other psychiatric or neurological prescriptions, which may affect outcomes. It is also notable that most trials include a relatively small number of participants or last for a short duration. Altogether, these limitations are likely to contribute to negative results of lithium treatment.

Another limitation of these clinical trials may be the use of lithium salts that have a high affinity for binding to Aβ fibrils and oligomers (13). LiO with the lowest ionization capacity among 16 tested lithium salts can evade amyloid sequestration in AD brains. Low dose treatment of LiO that maintains physiological range of Li levels in cortex and serum with no observed adverse effect prevents and even reverses AD pathology, neuroinflammatory signs and cognitive decline (94).

LiO dissociates in an aqueous solution to release lithium cations and orotic acid (OA), a precursor in pyrimidine biosynthesis (95). OA is generated by mitochondrial dihydroorotate dehydrogenase (DHODH) and converted to uridine monophosphate (UMP) by cytoplasmic UMP synthase. OA is naturally present in a normal diet, particularly in milk and dairy products, and is converted to uridine for use in the pyrimidine salvage pathway, primarily in the liver, kidney, and erythrocytes (96-99). Interestingly, OA treatment improves learning behavior in rats, promotes neuroprotective effect for gerbils and cats under transient cerebral ischemia (100-102). The neurological effects are generally attributed to the role of OA as a precursor for pyrimidine nucleotides and RNA. OA forms chemical complexes and salts with various metal ions (e.g., Mg^{2+}, Zn^{2+}, Ca^{2+}, and K^+) and organic cations (e.g., choline and carnitine), as well as coordination compounds with platinum, palladium, and tin. These chemical properties allow OA to be used as a carrier to deliver these ligands for medicinal purposes (103, 104). Therefore, OA may contribute to neuroprotective effects by supporting mitochondrial metabolism, facilitating RNA synthesis, and slowing renal clearance during long-term use, independently of lithium ions.

CONCLUSION

Lithium is a modulator acting across multiple pathways in AD, and lithium treatment generally ameliorates most pathological conditions of AD, including Aβ deposition, phospho-tau accumulation, neuroinflammation, and synaptic dysfunction. However, it is challenging to determine appropriate thera-

peutic dosages of lithium salts, because commonly prescribed lithium salts, such as lithium carbonate and lithium chloride, have high ionization capacity and show toxic side effects even at low doses. Recently, it has been revealed that amyloid plaques sequester and deplete lithium in the brain, thereby accelerating AD pathology. Lithium deficiency induced by dietary restriction of lithium may promote Aβ and tau aggregation, neuroinflammation, and the loss of synapses, axons, and myelin. This lithium depletion may contribute to neuropathological changes that begin years before AD symptoms become obvious. Lithium orotate, with lower conductivity and reduced binding to amyloid, prevents and even reverses pathological progression in AD and aging mice. While these findings suggest that lithium may have potential benefits, it is necessary to rigorously evaluate the clinical effectiveness of lithium in AD treatment by using unambiguous biomarkers and diagnostic criteria.

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CONFLICTS OF INTEREST

The authors have no conflicting interests.

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