Lithium Shows Potential as a Treatment for Alzheimer Disease

Key Takeaways

- Lithium deficiency in the brain may be an early event in Alzheimer's disease progression, potentially driving the disease.
- Lithium plays a critical role in protecting neurons, regulating cellular signaling, and maintaining healthy nerve cell communication.
- The study found that lithium depletion was linked to amyloid plaque sequestration and cognitive decline in both human and animal models.
- Restoring lithium levels in the brain showed promise in reversing pathological protein buildup and preserving neural structures in AD models.
- Controlled human clinical trials are essential to determine the viability of lithium supplementation as a treatment for Alzheimer's disease.

Harvard researchers reveal lithium deficiency as a potential early driver of Alzheimer's disease, suggesting new treatment avenues for patients.

Lithium may be a potential treatment for patients with Alzheimer disease (AD), according to researchers at Harvard Medical School (HMS). Their 10-year findings inform clinical understanding of the neurological changes leading to AD, highlighting the significant impact of lithium deficiency in the brain.1

Alzheimer Disease

AD is a highly prevalent neurodegenerative disorder that affects approximately 400 million people worldwide and 6.9 million in the United States. It refers to a variety of brain abnormalities, such as clumps of the protein amyloid-β, neurofibrillary tangles of the protein tau, and loss of REST, which lead to brain cell death and shrinkage. AD is associated with a variety of symptoms not limited to memory loss; difficulty with thinking, reasoning, or decision-making; changes in behavior or personality; and impaired preserved skills, which impact the ability to read books, tell stories, share memories, or engage in activities such as dancing, singing, drawing, or doing crafts.1,2

Treatment for AD is traditionally focused on lessening damage and reducing the rate of cognitive decline. This leaves patients with limited choices, merely delaying the inevitable onset of AD and worsening disease. However, emerging research highlights a novel treatment opportunity: lithium.1

Lithium and Alzheimer Disease

Lithium is a naturally occurring trace element in the human body and brain, best known for its long-standing use as a treatment for mood disorders such as bipolar disorder. In the brain, lithium plays a critical role in protecting neurons from damage, regulating cellular signaling, and maintaining healthy communication between nerve cells. It influences key enzymes and pathways—including glycogen synthase kinase 3β (GSK3β)—that are directly tied to protein accumulation, inflammation, and cell survival.1,3

Although small amounts of lithium are obtained through diet and water, its levels in the brain are tightly regulated. Research has shown that even subtle deficiencies can impair the resilience of brain cells, reducing their ability to resist injury, oxidative stress, and toxic protein buildup.1,3

Emerging evidence suggests that lithium may do far more than stabilize mood. In AD, researchers found that lithium loss is not just a consequence of brain damage but an early event that may actively drive disease progression. In both human tissue and animal models, reduced lithium availability was linked to the trapping of lithium by amyloid plaques and decreased uptake by neurons and other brain cells. 1,3

“The idea that lithium deficiency could be a cause of AD is new and suggests a different therapeutic approach,” Bruce Yakner, MD, PhD, senior author, professor of genetics and neurology in the Blavatnik Institute at HMS, said in the news release. Yakner was the first to demonstrate that amyloid-β is toxic in the 1990s.1

The Study

The researchers analyzed postmortem brain tissue from individuals with normal cognition, mild cognitive impairment (MCI), and AD. Using highly sensitive mass spectrometry, they measured lithium levels in the prefrontal cortex in regions with and without amyloid plaques and in the cerebellum and blood serum. They also tested the impact of dietary lithium depletion in healthy mice and in genetically engineered AD mouse models. Finally, they assessed whether supplementing with lithium orotate, a form of lithium with reduced amyloid binding, could reverse the effects.3

The Findings

Lithium was significantly reduced in the prefrontal cortex in people with MCI, an early stage of AD, and levels fell even further in AD brains due to sequestration by amyloid plaques. In mice, reducing brain lithium by about 50% triggered accelerated amyloid-β and tau buildup, neuroinflammation, synapse and myelin loss, and faster cognitive decline. These changes were partly driven by overactivation of the enzyme GSK3β.3

Single-nucleus RNA sequencing showed that lithium deficiency altered gene activity in multiple brain cell types, producing patterns that closely resembled those seen in human AD. Treatment with low-dose lithium orotate restored brain lithium levels, prevented the buildup of pathological proteins, preserved neural structures, and protected memory in both AD and aging wild-type mice.3

The results suggest that lithium depletion may be one of the earliest biochemical events in AD, potentially years before symptoms emerge. Restoring lithium levels could offer a way to halt or even reverse disease progression.3

What’s Next?

The researchers suggest that restoring brain lithium levels may offer a safe and accessible way to slow or prevent AD progression. They emphasize that although these findings are promising in animal models, controlled human clinical trials are essential to determine whether lithium supplementation could become a viable treatment option for patients at risk or in the early stages of the disease. If successful in humans, low-dose lithium orotate could become an inexpensive, widely accessible treatment to prevent or delay the onset of AD.1

“You have to be careful about extrapolating from mouse models, and you never know until you try it in a controlled human clinical trial,” Yankner said. “But so far the results are very encouraging.”1

REFERENCES

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