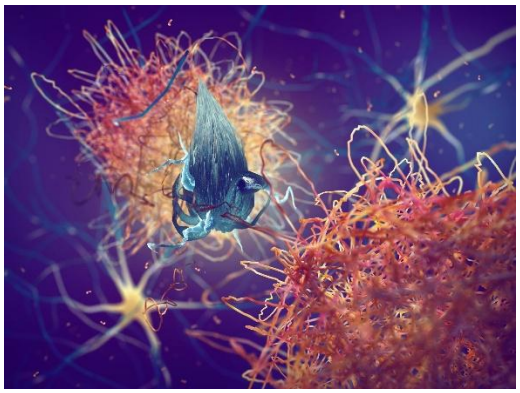
To Early Alzheimer's Changes Scientists Link Brain Lithium Loss

Researchers in the United States investigated how naturally occurring lithium in the brain is regulated and whether it plays a role in protecting against cognitive decline and Alzheimer's disease.

They found that reduced endogenous lithium contributes to early pathological changes in the progression of the disease, while restoring lithium levels with lithium orotate prevents brain damage and memory loss in mouse models, suggesting a potential preventive and therapeutic strategy for Alzheimer's.



Study

The researchers studied lithium levels in human brain and blood samples from people with no cognitive impairment, mild cognitive impairment, or Alzheimer's disease. They used a highly sensitive method called inductively coupled plasma mass spectrometry to measure lithium levels in the cortex, cerebellum, and serum.

Some brain samples were separated into areas with and without amyloid plaques using immunofluorescence, and lithium levels in these regions were compared. The accuracy of the measurements was confirmed using different sample sets, procedures, and blinded testing. They also mapped where lithium was located in the brain tissue.

In mouse studies, both healthy and Alzheimer's disease-prone strains were used. Some mice were fed a diet extremely low in lithium, while others received lithium supplements in their drinking water, either as lithium orotate or lithium carbonate.

Researchers monitored how much lithium the mice absorbed and its effects on the brain. They also examined how lithium binds to amyloid-β in the lab, noting that the lower conductivity of lithium orotate resulted in weaker binding compared to lithium carbonate. Memory and brain changes were assessed using behavioral tests and molecular analyses. All animal experiments were carefully controlled, ethically approved, and designed to match human lithium exposure levels.

Results

The study found that lithium levels were significantly lower in the brains of individuals with both mild cognitive impairment and Alzheimer's disease compared to those with no cognitive issues. However, serum levels of lithium were not significantly different.

This reduction was found specifically in the prefrontal cortex, a region heavily affected by the disease, but not in the cerebellum or in blood samples. Notably, lithium was found to be highly concentrated within amyloid-β plaques compared to the surrounding non-plaque regions, suggesting that plaques trap, or sequester, lithium, thereby depleting it from the rest of the brain tissue.

In mouse models, a lithium-deficient diet led to reduced lithium levels in the brain, particularly in Alzheimer's disease-prone strains. These mice showed increased amyloid-β accumulation, tau pathology, the loss of synapses and myelin, and signs of neuroinflammation, along with memory and cognitive impairments.

Conversely, lithium supplementation, especially with lithium orotate, restored brain lithium levels and prevented many Alzheimer's disease-related changes, including plaque buildup and inflammation. Lithium orotate was more effective than lithium carbonate at elevating lithium in the non-plaque brain tissue and did not show evidence of toxicity at the low doses used. By contrast, lithium carbonate showed greater sequestration in amyloid plaques and did not significantly improve pathology at the same low dose.

In laboratory tests, lithium orotate also showed weaker binding to amyloid-β proteins, which may allow it to better evade sequestration by plaques and improve its brain distribution. Overall, the results suggest that reduced lithium levels in the brain may contribute to the development of Alzheimer's disease, and restoring physiological lithium levels, especially with lithium orotate, could help protect against cognitive decline and Alzheimer's pathology.

Conclusion

This study provides strong evidence that endogenous lithium plays a key physiological role in maintaining brain health and protecting against Alzheimer's disease. In mouse models, normal physiological levels of lithium preserved cognition, reduced inflammation, and suppressed hallmark Alzheimer's disease-associated pathologies, such as amyloid-β accumulation, tau phosphorylation, and loss of synapses and myelin.

Lithium deficiency, on the other hand, impaired microglial function, increased inflammation, and disrupted gene expression in multiple brain cell types. Notably, lithium levels were consistently lower in the brains of humans with Alzheimer's disease, aligning with mouse model findings. Furthermore, single-nucleus RNA sequencing revealed that the gene expression changes caused by lithium deficiency in mouse brains overlapped significantly with those found in human brain tissue from patients with AD.

A key mechanism involves increased activity of the enzyme GSK3β under lithium deficiency, which elevates both total and activated levels of the kinase and contributes to neurodegeneration. Crucially, these pathological effects could be reversed in mice by treatment with GSK3β inhibitors.

Importantly, the study demonstrated that a low-dose lithium orotate treatment, keeping lithium in the physiological range, was effective in reversing the pathology of the disease in mice without detectable toxicity, addressing a major concern of standard lithium therapies.

The paper suggests that the limited success of past human trials may be due to issues with lithium formulations, such as the use of salts like lithium carbonate with high levels of amyloid

binding. Overall, lithium deficiency may underlie early neurodegenerative changes, making it a promising target for the prevention and treatment of Alzheimer's disease.

Source:

https://www.news-medical.net/news/20250807/Scientists-link-brain-lithium-loss-to-early-Alzheimere28099s-changes.aspx