Scientists reverse Alzheimer's in mice and restore memory: Study

The research was led by KalyChaubey, PhD, of the Pieper Laboratory and published on December 22 in Cell Reports Medicine. By examining both human Alzheimer's brain tissue and multiple preclinical mouse models, the team identified a key biological failure at the center of the disease.

Washington DC: Alzheimer's has long been considered irreversible, but new research challenges that assumption. Scientists discovered that severe drops in the brain's energy supply help drive the disease, and restoring that balance can reverse damage, even in advanced cases.

In mouse models, treatment repaired brain pathology, restored cognitive function, and normalised Alzheimer's biomarkers. The results offer fresh hope that recovery may be possible.

A study reveals that restoring the brain's energy balance may not only slow Alzheimer's disease but also reverse it.

For more than 100 years, Alzheimer's disease (AD) has been widely viewed as a condition that cannot be undone. Because of this belief, most scientific efforts have focused on preventing the disease or slowing its progression, rather than attempting to restore lost brain function.

Even after decades of research and billions of dollars in investment, no drug trial for Alzheimer's has ever been designed with the goal of reversing the disease and recovering cognitive abilities.

That long-held assumption is now being challenged by researchers from University Hospitals, Case Western Reserve University, and the Louis Stokes Cleveland VA Medical Center.

Their work set out to answer a bold question: Can brains already damaged by advanced Alzheimer's recover?

New Study Targets Brain Energy Failure

The research was led by KalyChaubey, PhD, of the Pieper Laboratory and published on December 22 in Cell Reports Medicine. By examining both human Alzheimer's brain tissue and multiple preclinical mouse models, the team identified a key biological failure at the center of the disease.

They found that the brain's inability to maintain normal levels of a critical cellular energy molecule called NAD+ plays a major role in driving Alzheimer's.

Importantly, maintaining proper NAD+ balance was shown to not only prevent the disease but also reverse it in experimental models.

NAD+ levels naturally decline throughout the body, including the brain, as people age. When NAD+ drops too low, cells lose the ability to carry out essential processes needed for normal function and survival.

The researchers discovered that this decline is far more severe in the brains of people with Alzheimer's. The same pattern was seen in mouse models of the disease.

How Alzheimer's Was Modelled in the Lab

Although Alzheimer's occurs only in humans, scientists study it using specially engineered mice that carry genetic mutations known to cause the disease in people.

In this study, researchers used two such models. One group of mice carried multiple human mutations affecting amyloid processing, while the other carried a human mutation in the tau protein.

Amyloid and tau abnormalities are among the earliest and most significant features of Alzheimer's.

In both mouse models, these mutations led to widespread brain damage that closely mirrors the human disease. This included breakdown of the blood-brain barrier, damage to nerve fibers, chronic inflammation, reduced formation of new neurons in the hippocampus, weakened communication between brain cells, and extensive oxidative damage.

The mice also developed severe memory and cognitive problems similar to those seen in people with Alzheimer's.

Testing Whether Alzheimer's Damage Could Be Reversed

After confirming that NAD+ levels dropped sharply in both human and mouse Alzheimer's brains, the team explored two possibilities.

They tested whether maintaining NAD+ balance before symptoms appeared could prevent Alzheimer's, and whether restoring that balance after the disease had already progressed could reverse it.

This approach was built on the group's earlier work published in Proceedings of the National Academy of Sciences USA, which showed that restoring NAD+ balance led to both structural and functional recovery after severe, long-lasting traumatic brain injury.

In the current study, the researchers used a well-characterised pharmacologic compound called P7C3-A20, developed in the Pieper laboratory, to restore NAD+ balance.

Full Cognitive Recovery Observed in Advanced Disease

The results were striking. Preserving NAD+ balance protected mice from developing Alzheimer's, but even more surprising was what happened when treatment began after the disease was already advanced.

In those cases, restoring NAD+ balance allowed the brain to repair the major pathological damage caused by the genetic mutations.

Both mouse models showed complete recovery of cognitive function. This recovery was also reflected in blood tests, which showed normalised levels of phosphorylated tau 217, a recently approved clinical biomarker used to diagnose Alzheimer's in people.

These findings provided strong evidence of disease reversal and highlighted a potential biomarker for future human trials.

Researchers Express Cautious Optimism

"We were very excited and encouraged by our results," said Andrew A. Pieper, MD, PhD, senior author of the study and Director of the Brain Health Medicines Center, Harrington Discovery Institute at UH. "Restoring the brain's energy balance achieved pathological and functional recovery in both lines of mice with advanced Alzheimer's.

Seeing this effect in two very different animal models, each driven by different genetic causes, strengthens the idea that restoring the brain's NAD+ balance might help patients recover from Alzheimer's."

Dr. Pieper also holds the Morley-Mather Chair in Neuropsychiatry at UH and the CWRU Rebecca E. Barchas, MD, DLFAPA, University Professorship in Translational Psychiatry. He serves as Psychiatrist and Investigator in the Louis Stokes VA Geriatric Research Education and Clinical Center (GRECC).

The findings suggest a fundamental change in how Alzheimer's could be approached in the future. "The key takeaway is a message of hope -- the effects of Alzheimer's disease may not be inevitably permanent," said Dr. Pieper. "The damaged brain can, under some conditions, repair itself and regain function."

Dr. Chaubey added, "Through our study, we demonstrated one drug-based way to accomplish this in animal models, and also identified candidate proteins in the human AD brain that may relate to the ability to reverse AD."

Why This Approach Differs From Supplements

Dr. Pieper cautioned against confusing this strategy with over-the-counter NAD+-precursors. He noted that such supplements have been shown in animal studies to raise NAD+ to dangerously high levels that promote cancer.

The method used in this research relies instead on P7C3-A20, a pharmacologic agent that helps cells maintain healthy NAD+ balance during extreme stress, without pushing levels beyond their normal range.

"This is important when considering patient care, and clinicians should consider the possibility that therapeutic strategies aimed at restoring brain energy balance might offer a path to disease recovery," said Dr. Pieper.

The research also opens the door to additional studies and eventual testing in people. The technology is currently being commercialized by Glengary Brain Health, a Cleveland-based company co-founded by Dr. Pieper.

News Source:

https://health.economictimes.indiatimes.com/news/industry/scientists-reverse-alzheimers-in-mice-and-restore-memory-study/126228637