Boosting brain protein levels may slow decline from Alzheimer's

September 11 2024

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A study published in the journal *Brain* shows that increases in protein levels with new Alzheimer's drugs can explain the slowing of cognitive impairment at least as well as the reduction in amyloid plaques.

During a study challenging the idea that newly approved monoclonal antibodies reduce cognitive decline in Alzheimer's patients by clearing amyloid, University of Cincinnati researchers found that the unintended increase in levels of a critical brain protein correlates equally well with cognitive benefits.

For decades, the prevailing theory in the field has stated that a protein made up of 42 amino acids called amyloid-beta 42 (Aβ42) hardens into clumps called amyloid plaques, and those plaques damage the brain, causing Alzheimer's disease.

Led by UC's Alberto Espay, MD, the team have hypothesized that normal, soluble Aβ42 in the brain is crucial for neuron health and that the loss of Aβ42, rather than the buildup of plaques, drives Alzheimer's. This includes published research that suggests dementia occurs not when plaque levels are high but when Aβ42 levels drop very low.

According to Espay's research, the transformation of Aβ42 into plaques appears to be the brain's normal response to biological, metabolic or infectious stress.

"Most of us will accrue amyloid plaques in our brains as we age, and yet very few of us with plaques go on to develop dementia," said Espay, professor of neurology in the UC College of Medicine and director and endowed chair of the James J. and Joan A. Gardner Family Center for Parkinson's Disease and Movement Disorders at the UC Gardner Neuroscience Institute.

"Yet the plaques remain the center of our attention in biomarker development and therapeutic strategies."

Recently, several new monoclonal antibody medications designed to remove amyloid from the brain were approved after showing they

lessened cognitive decline in clinical trials.

Espay and his colleagues noticed that these drugs unintentionally increased levels of Aβ42.

"Amyloid plaques don't cause Alzheimer's, but if the brain makes too much of it while defending against infections, toxins or biological changes, it can't produce enough Aβ42, causing its levels to drop below a critical threshold," Espay explained. "That's when dementia symptoms emerge."

The team analyzed data from nearly 26,000 patients enrolled in 24 randomized clinical trials of these new antibody treatments, assessing cognitive impairment and differences in levels of Aβ42 before and after treatment. They found that higher levels of Aβ42 after treatment were independently associated with slower cognitive impairment and clinical decline.

"All stories have two sides—even the one we have told ourselves about how anti-amyloid treatments work: by lowering amyloid," Espay said.

"In fact, they also raise the levels of Aβ42. Even if this is unintended, it is why there may be a benefit. Our study shows that we can predict changes in cognitive outcomes in anti-amyloid trials at least as well by the increases in Aβ42 as by the decreases in amyloid."

Espay said these findings fit well into his larger hypothesis about the root cause of Alzheimer's, as increasing levels of Aβ42 appear to improve cognition.

"If the problem with Alzheimer's is the loss of the normal protein, then increasing it should be beneficial, and this study showed that it is," he said. "The story makes sense: Increasing Aβ42 levels to within the

normal range is desirable."

However, Espay believes these results also present a conundrum for clinicians because removing amyloid from the brain is toxic and may cause the brain to shrink faster after antibody treatment.

"Do we give patients an anti-protein treatment to increase their protein levels? I think the end, increasing Aβ42, doesn't justify the means, decreasing amyloid," Espay said. Therapies that directly increase Aβ42 levels without targeting amyloid are a focus of research for Espay and his group.

Other co-authors of the study include UC's Jesus Abanto, Alok K. Dwivedi of Texas Tech University and Bruno P. Imbimbo of Chiesi Farmaceutici of Parma, Italy

More information: Alberto Espay et al, Increases in Aß42 Slow Cognitive and Clinical Decline in Alzheimer's Disease Trials, *Brain* (2024). DOI: 10.1093/brain/awae216

Provided by University of Cincinnati