New study reveals why defense against brain corrosion declines in people with Alzheimer's disease

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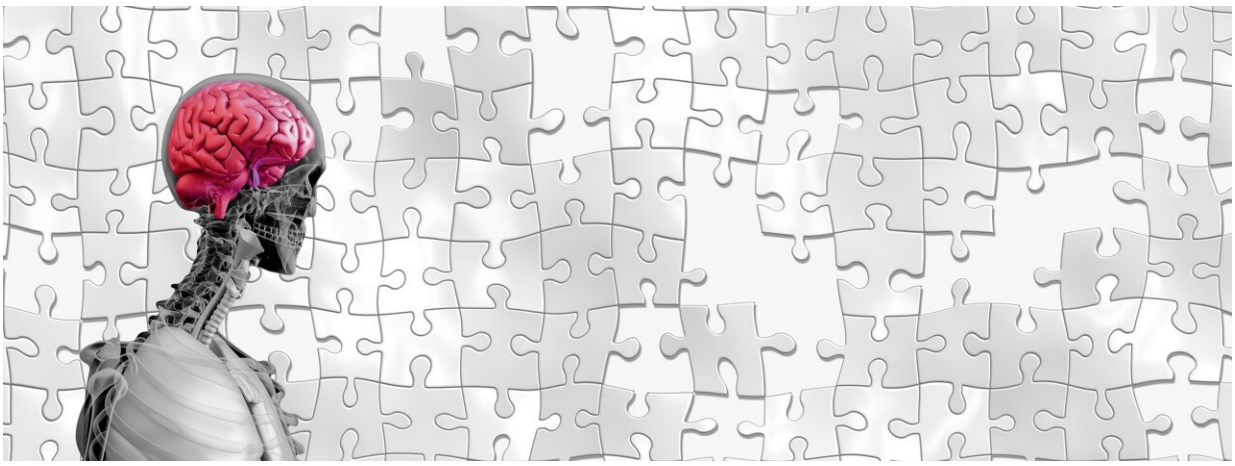

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A new study by researchers at Case Western Reserve University revealed that the progression of Alzheimer's disease (AD) can be slowed by suppressing a specific protein in the brain that causes corrosion.

A main pathogenic initiator of AD and related dementias is oxidative stress, which corrodes the brain, called oxidative damage.

David E. Kang, the Howard T. Karsner Professor in Pathology at the Case Western Reserve School of Medicine and the study's lead

researcher, said they've identified for the first time a cause for the loss of so-called "oxidative damage defense" in AD.

A protein called Nuclear factor erythroid 2-related factor 2 (Nrf2) is regularly activated in response to oxidative stress to protect the brain from oxidative damage. But in the brain of someone with AD, Nrf2 defense against oxidative stress declines. How that occurs in AD was unknown.

The study, published in the journal *PNAS*, found that a protein called Slingshot Homolog-1, or SSH1, stops Nrf2 from carrying out its protective biological activity.

Genetically eliminating SSH1 increases Nrf2 activation and slows the development of oxidative damage and buildup of toxic plaques and tangles in the brain—both risk factors for AD. As a result, the regular connections between brain cells are maintained and degeneration of brain nerve cells is avoided, they found.

The finding is significant because most clinical trials have been conducted with people with advanced dementia. The tests focused mainly on managing and reducing symptoms to enhance daily functioning and quality of life.

"Focusing on clinical trials in the early stages of AD increases the likelihood of success," Kang said. "In the upcoming five years, I also think we'll see modest improvements in treatments for Alzheimer's disease, which will help slow AD's course."

For example, clinical trials for Leqembi—medication for early AD recently approved by the U.S. Food and Drug Administration—have shown somewhat promising results to slow progression of the disease.

Case Western Reserve is among those working on SSH1 inhibitor compounds as potential neuroprotective medicines.

"Many promising drug candidates are certainly in the pipeline," Kang said.

More information: Sara Cazzaro et al, Slingshot homolog-1–mediated Nrf2 sequestration tips the balance from neuroprotection to neurodegeneration in Alzheimer's disease, *Proceedings of the National Academy of Sciences* (2023). DOI: 10.1073/pnas.2217128120

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