New molecule reverses Alzheimer's-like memory decline

August 4 2020

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A drug candidate developed by Salk researchers, and previously shown to slow aging in brain cells, successfully reversed memory loss in a mouse model of inherited Alzheimer's disease. The new research,

published online in July 2020 in the journal *Redox Biology*, also revealed that the drug, CMS121, works by changing how brain cells metabolize fatty molecules known as lipids.

"This was a more rigorous test of how well this compound would work in a therapeutic setting than our previous studies on it," says Pamela Maher, a senior staff scientist in the lab of Salk Professor David Schubert and the senior author of the new paper. "Based on the success of this study, we're now beginning to pursue clinical trials."

Over the last few decades, Maher has studied how a chemical called fisetin, found in fruits and vegetables, can improve memory and even prevent Alzheimer's-like disease in mice. More recently, the team synthesized different variants of fisetin and found that one, called CMS121, was especially effective at, improving the animals' memory, and slowing the degeneration of brain cells.

In the new study, Maher and colleagues tested the effect of CMS121 on mice that develop the equivalent of Alzheimer's disease. Maher's team gave a subset of the mice daily doses of CMS121 beginning at 9 months old—the equivalent of middle age in people, and after the mice have already begun to show learning and memory problems. The timing of the lab's treatment is akin to how a patient who visits the doctor for cognitive problems might be treated, the researchers say.

After three months on CMS121, at 12 months old, the mice—both treated and untreated—were given a battery of memory and behavior tests. In both types of tests, mice with Alzheimer's-like disease that had received the drug performed equally well as healthy control animals, while untreated mice with the disease performed more poorly.

To better understand the impact of CMS121, the team compared the levels of different molecules within the brains of the three groups of

mice. They discovered that when it came to levels of lipids—fatty molecules that play key roles in cells throughout the body—mice with the disease had several differences compared to both healthy mice and those treated with CMS121. In particular, the researchers pinpointed differences in something known as lipid peroxidation—the degradation of lipids that produces free radical molecules that can go on to cause cell damage. Mice with Alzheimer's-like disease had higher levels of lipid peroxidation than either healthy mice or those treated with CMS121.

"That not only confirmed that lipid peroxidation is altered in Alzheimer's, but that this drug is actually normalizing those changes," says Salk postdoctoral fellow Gamze Ates, first author of the new paper.

The researchers went on to show that CMS121 lowered levels of a lipid-producing molecule called fatty acid synthetase (FASN), which, in turn, lowered levels of lipid peroxidation. When the group analyzed levels of FASN in brain samples from human patients who had died of Alzheimer's, they found that the patients had higher amounts of the FASN protein than similarly aged controls who were cognitively healthy, which suggests FASN could be a drug target for treating Alzheimer's disease.

While the group is pursuing clinical trials, they hope other researchers will explore additional compounds that may treat Alzheimer's by targeting FASN and lipid peroxidation.

"There has been a big struggle in the field right now to find targets to go after," says Maher. "So, identifying a new target in an unbiased way like this is really exciting and opens lots of doors."

More information: Gamze Ates et al, CMS121, a fatty acid synthase inhibitor, protects against excess lipid peroxidation and inflammation and alleviates cognitive loss in a transgenic mouse model of Alzheimer's

disease, *Redox Biology* (2020). DOI: 10.1016/j.redox.2020.101648