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Study suggests iron is at core of Alzheimer's disease

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Alzheimer's disease has proven to be a difficult enemy to defeat. After all, aging is the No. 1 risk factor for the disorder, and there's no stopping that.

Most researchers believe the disease is caused by one of two proteins, one called tau, the other beta-amyloid. As we age, most scientists say, these proteins either disrupt signaling between neurons or simply kill them.

Now, a new UCLA study suggests a third possible cause: iron accumulation.

Dr. George Bartzokis, a professor of psychiatry at the Semel Institute for Neuroscience and Human Behavior at UCLA and senior author of the study, and his colleagues looked at two areas of the brain in patients with Alzheimer's. They compared the hippocampus, which is known to be damaged early in the disease, and the thalamus, an area that is generally not affected until the late stages. Using sophisticated brain-imaging techniques, they found that iron is increased in the hippocampus and is associated with tissue damage in that area. But increased iron was not found in the thalamus.

The research appears in the August edition of the *Journal of Alzheimer's Disease*.

While most Alzheimer's researchers focus on the buildup of tau or beta-

amyloid that results in the signature plaques associated with the disease, Bartzokis has long argued that the breakdown begins much further "upstream." The destruction of myelin, the fatty tissue that coats nerve fibers in the brain, he says, disrupts communication between neurons and promotes the buildup of the plaques. These amyloid plaques in turn destroy more and more myelin, disrupting brain signaling and leading to cell death and the classic clinical signs of Alzheimer's.

Myelin is produced by cells called oligodendrocytes. These cells, along with myelin, have the highest levels of iron of any cells in the brain, Bartzokis says, and circumstantial evidence has long supported the possibility that brain iron levels might be a risk factor for age-related diseases like Alzheimer's. Although iron is essential for cell function, too much of it can promote oxidative damage, to which the brain is especially vulnerable.

In the current study, Bartzokis and his colleagues tested their hypothesis that elevated tissue iron caused the tissue breakdown associated with Alzheimer's disease. They targeted the vulnerable hippocampus, a key area of the brain involved in the formation of memories, and compared it to the thalamus, which is relatively spared by Alzheimer's until the very late stages of disease.

The researchers used an MRI technique that can measure the amount of brain iron in ferritin, a protein that stores iron, in 31 patients with Alzheimer's and 68 healthy control subjects.

In the presence of diseases like Alzheimer's, as the structure of cells breaks down, the amount of water increases in the brain, which can mask the detection of iron, according to Bartzokis.

"It is difficult to measure iron in tissue when the tissue is already damaged," he said. "But the MRI technology we used in this study

allowed us to determine that the increase in iron is occurring together with the tissue damage. We found that the amount of iron is increased in the hippocampus and is associated with tissue damage in patients with Alzheimer's but not in the healthy older individuals—or in the thalamus. So the results suggest that iron accumulation may indeed contribute to the cause of Alzheimer's disease."

But it's not all bad news from this study, Bartzokis noted.

"The accumulation of iron in the brain may be influenced by modifying environmental factors, such as how much red meat and iron dietary supplements we consume and, in women, having hysterectomies before menopause," he said.

In addition, he noted, medications that chelate and remove iron from tissue are being developed by several pharmaceutical companies as treatments for the disorder. This MRI technology may allow doctors to determine who is most in need of such treatments.

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