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Early sign of Alzheimer's reversed in lab

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One of the earliest known impairments caused by Alzheimer's disease - loss of sense of smell – can be restored by removing a plaque-forming protein in a mouse model of the disease, a study led by a Case Western Reserve University School of Medicine researcher finds.

The study confirms that the protein, called amyloid beta, causes the loss.

"The evidence indicates we can use the sense of smell to determine if someone may get Alzheimer's disease, and use changes in sense of smell to begin treatments, instead of waiting until someone has issues learning and remembering," said Daniel Wesson, assistant professor of neuroscience at Case Western Reserve and lead investigator. "We can also use smell to see if therapies are working."

A description of the research is published in the Nov. 2 issue of The *Journal of Neuroscience*.

Smell loss can be caused by a number of ailments, exposures and injuries; but since the 1970s, it has been identified as an early sign of this disease. The new research shows how and where in the brain this happens, and that the impairment it can be treated.

"Understanding smell loss, we think, will hold some clues about how to slow down this disease," Wesson said.

There is currently no effective treatment or cure for the disease, marked by eroding senses, cognition and coordination, leading to death.

Currently 5.3 million Americans suffer from Alzheimer's and the number is expected to triple to 16 million by 2050, according to the Alzheimer's Association.

Wesson worked with Anne H. Borkowski, a researcher at the Nathan S. Kline Institute in Orangeburg, N.Y., Gary E. Landreth, professor of neuroscience at Case Western Reserve School of Medicine, and Ralph A. Nixon, Efrat Levy and Donald A. Wilson, of the New York University School of Medicine.

They found that just a tiny amount of amyloid beta – too little to be seen on today's brain scans - causes smell loss in mouse models.

Amyloid beta plaque accumulated first in parts of the brain associated with smell, well before accumulating in areas associated with cognition and coordination.

Early on, the olfactory bulb, where odor information from the nose is processed, became hyperactive.

Over time, however, the level of amyloid beta increased in the olfactory bulb and the bulb became hypoactive. Despite spending more time sniffing, the mice failed to remember smells and became incapable of telling the difference between odors.

The same pattern is seen in people with the disease. They become unresponsive to smells as they age.

While losses in the olfactory system occurred, the rest of the mouse model brain, including the hippocampus, which is a center for memory, continued to act normally early in the disease stage.

"This shows the unique vulnerability of the olfactory system to the

pathogenesis of Alzheimer's disease," Wesson said.

The team then sought to reverse the effects. Mice were given a synthetic liver x-receptor agonist, a drug that clears amyloid beta from the brain. After two weeks on the drug, the mice could process smells normally.

After withdrawal of the drug for one week, impairments returned.

Wesson and his team are now following-up on these discoveries to determine how amyloid spreads throughout the brain, to learn methods to slow disease progression.

Provided by Case Western Reserve University