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Substance involved in Alzheimer's can reverse paralysis in mice with multiple sclerosis

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A molecule widely assailed as the chief culprit in Alzheimer's disease unexpectedly reverses paralysis and inflammation in several distinct animal models of a different disorder — multiple sclerosis, Stanford University School of Medicine researchers have found.

This surprising discovery, which will be reported in a study to be published online Aug. 1 as the cover feature in *Science Translational Medicine*, comes on the heels of the recent failure of a large-scale clinical trial aimed at slowing the progression of Alzheimer's disease by attempting to clear the much-maligned molecule, known as A-beta, from Alzheimer's patients' bloodstreams. While the findings are not necessarily applicable to the study of A-beta's role in the pathology of that disease, they may point to promising new avenues of treatment for multiple sclerosis.

The short protein snippet, or peptide, called A-beta (or beta-amyloid) is quite possibly the single most despised substance in all of brain research. It comes mainly in two versions differing slightly in their length and biochemical properties. A-beta is the chief component of the amyloid plaques that accumulate in the brains of Alzheimer's patients and serve as an identifying hallmark of the neurodegenerative disorder.

A-beta deposits also build up during the normal aging process and after brain injury. Concentrations of the peptide, along with those of the

precursor protein from which it is carved, are found in multiple-sclerosis lesions as well, said Lawrence Steinman, MD, the new study's senior author. In a lab dish, A-beta is injurious to many types of cells. And when it is administered directly to the brain, A-beta is highly inflammatory.

Yet little is known about the physiological role A-beta actually plays in Alzheimer's — or in MS, said Steinman, a professor of neurology and neurological sciences and of pediatrics and a noted multiple-sclerosis researcher. He, first author Jacqueline Grant, PhD, and their colleagues set out to determine that role in the latter disease. (Grant was a graduate student in Steinman's group when the work was done.)

Multiple sclerosis, an inflammatory autoimmune disease, occurs when immune cells invade the brain and spinal cord and attack the insulating coatings of nerve cells' long, cable-like extensions called axons. Damage to these coatings, composed largely of a fatty substance called myelin, disrupts the transmission of signals that ordinarily travel long distances down axons to junctions with other nerve cells. This signal disruption can cause blindness, loss of muscle control and difficulties with speech, thought and attention.

Previous research by Steinman, who is also the George A. Zimmerman Professor, and others showed that both A-beta and its precursor protein are found in MS lesions. In fact, the presence of these molecules along an axon's myelinated coating is an excellent marker of damage there.

Given the peptide's nefarious reputation, Steinman and his associates figured that A-beta was probably involved in some foul play with respect to MS. To find out, they relied on a mouse model that mimics several features of multiple sclerosis — including the autoimmune attack on myelinated sections of the brain that causes MS.

Steinman had, some years ago, employed just such a mouse model in research that ultimately led to the development of natalizumab (marketed as Tysabri), a highly potent MS drug. That early work proved that dialing down the activation and proliferation of immune cells located outside the central nervous system (which is what natalizumab does) could prevent those cells from infiltrating and damaging nerve cells in the CNS.

Knowing that immunological events outside the brain can have such an effect within it, the Stanford scientists were keen on seeing what would happen when they administered A-beta by injecting it into a mouse's belly, rather than directly to the brain.

"We figured it would make it worse," Steinman said.

Surprisingly, the opposite happened. In mice whose immune systems had been "trained" to attack myelin, which typically results in paralysis, A-beta injections delivered before the onset of symptoms prevented or delayed the onset of paralysis. Even when the injections were given after the onset of symptoms, they significantly lessened the severity of, and in some cases reversed, the mice's paralysis.

Steinman asked Grant to repeat the experiment. She did, and got the same results.

His team then conducted similar experiments using a different mouse model: As before, they primed the mice's immune cells to attack myelin. But rather than test the effects of A-beta administration, the researchers harvested the immune cells about 10 days later, transferred them by injection to another group of mice that did not receive A-beta and then analyzed this latter group's response. The results mirrored those of the first set of experiments, proving that A-beta's moderating influence on the debilitating symptoms of the MS-like syndrome has nothing to do

with A-beta's action within the brain itself, but instead is due to its effect on immune cells before they penetrate the brain.

Sophisticated laboratory tests showed that A-beta countered not only visible symptoms such as paralysis, but also the increase in certain inflammatory molecules that characterizes multiple-sclerosis flare-ups. "This is the first time A-beta has been shown to have anti-inflammatory properties," said Steinman.

Inspection of the central nervous systems of the mice with the MS-resembling syndrome showed fewer MS-like lesions in the brains and spinal cords of treated mice than in those not given A-beta. There was also no sign of increased Alzheimer's-like plaques in the A-beta-treated animals. "We weren't giving the mice Alzheimer's disease" by injecting A-beta into their bellies, said Grant.

In addition, using an advanced cell-sorting method called flow cytometry, the investigators showed A-beta's strong effects on the immune system composition outside the brain. The numbers of immune cells called B cells were significantly diminished, while those of two other immune-cell subsets — myeloid cells and memory T-helper cells — increased.

"At this point we wanted to find out what would happen if we tried pushing A-beta levels down instead of up," Grant said. The researchers conducted a different set of experiments, this time in mice that lacked the gene for A-beta's precursor protein, so that they could produce neither the precursor nor A-beta. These mice, when treated with myelin-sensitized immune cells to induce the MS-like state, developed exacerbated symptoms and died faster and more frequently than normal mice who underwent the same regimen.

Lennart Mucke, MD, director of the Gladstone Institute of Neurological

Disease in San Francisco and a veteran Alzheimer's researcher, noted that while A-beta's toxicity within the brain has been established beyond reasonable doubt, many substances made in the body can have vastly different functions under different circumstances.

"A-beta is made throughout our bodies all of the time. But even though it's been studied for decades, its normal function remains to be identified," said Mucke, who is familiar with Steinman's study but wasn't involved in it. "Most intriguing, to me, is this peptide's potential role in modulating immune activity outside the brain."

The fact that the protection apparently conferred by A-beta in the mouse model of multiple sclerosis doesn't require its delivery to the brain but, rather, can be attributed to its immune-suppressing effect in the body's peripheral tissues is likewise intriguing, suggested Steinman.

"There probably is a multiple-sclerosis drug in all this somewhere down the line," he said.

Provided by Stanford University Medical Center

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