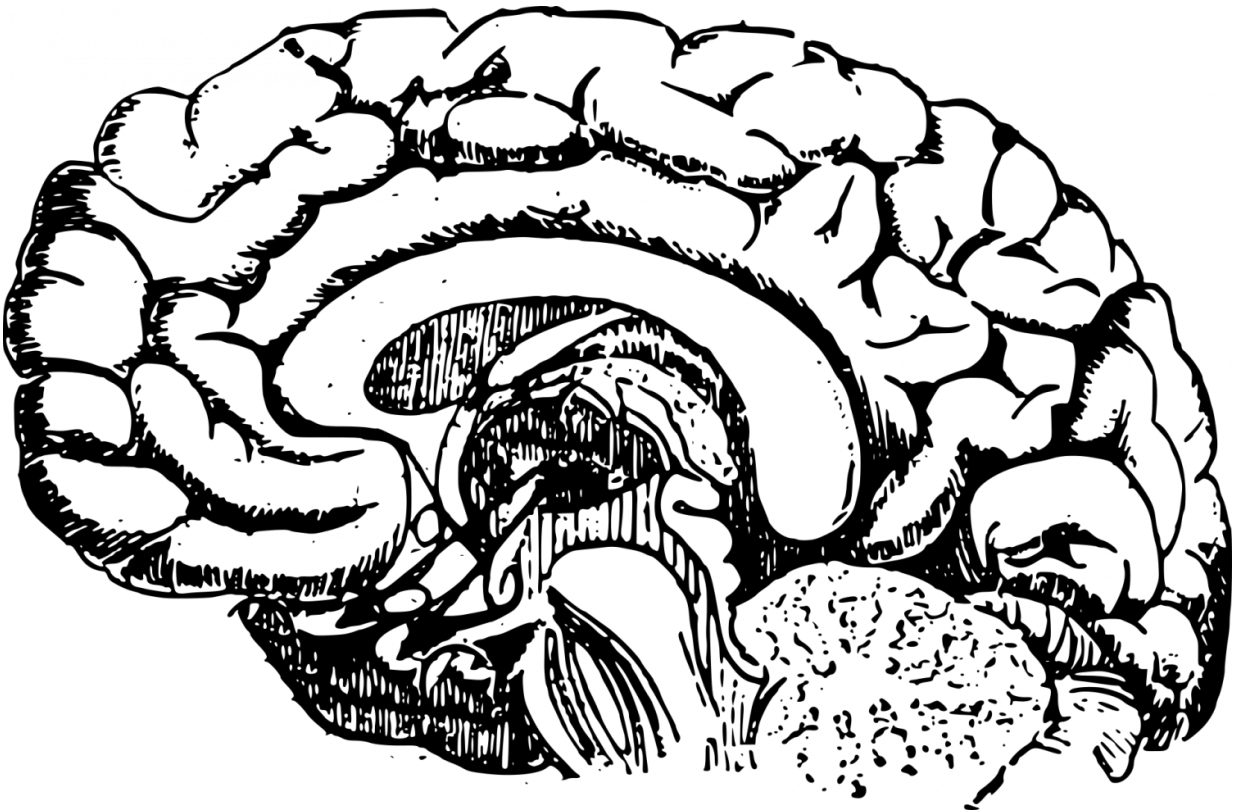


Amyloid beta protein protects brain from herpes infection by entrapping viral particles

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A Massachusetts General Hospital (MGH) study has found the mechanism by which amyloid beta (A-beta) - the protein deposited into plaques in the brains of patients with Alzheimer's disease—protects from the effects of herpes viruses commonly found in the brain. Along

with another study appearing in the same July 11 issue of *Neuron*, which found elevated levels of three types of herpes viruses in the brains of patients with Alzheimer's disease, the MGH team's results support a potential role for viral infection in accelerating A-beta deposition and Alzheimer's progression.

"There have been multiple epidemiological studies suggesting people with [herpes](#) infections are at higher risk for Alzheimer's disease, along with the most recent findings from Icahn School of Medicine at Mt. Sinai that are being published with our study," says Rudolph Tanzi, Ph.D., director of the Genetics and Aging Research Unit in the MassGeneral Institute for Neurodegenerative Disease (MIND) and co-corresponding author of the *Neuron* paper. "Our findings reveal a simple and direct mechanism by which herpes infections trigger the deposition of [brain](#) amyloid as a defense response in the brain. In this way, we have merged the [infection](#) hypothesis and amyloid hypothesis into one 'Antimicrobial Response Hypothesis' of Alzheimer's disease."

Previous studies led by Tanzi and co-corresponding author Robert Moir, Ph.D., also of the MIND Genetics and Aging Research Unit, found evidence indicating that A-beta—long thought to be useless "metabolic garbage—was an antimicrobial protein of the body's innate immune system, capable of protecting animal models and cultured human brain cells from dangerous infections. Given that brain infection with herpes simplex—the virus that causes cold sores—is known to increase with aging, leading to almost universal presence of that and other herpes strains in the brain by adulthood, the MGH team set out to find whether A-beta could protect against [herpes infection](#) and, if so, the mechanism by which such protection takes place.

After first finding that transgenic mice engineered to express human A-beta survive significantly longer after injections of herpes simplex into their brains than do nontransgenic mice, the researchers found that A-

beta inhibited infection of cultured human brain cells with herpes simplex and two other herpes strains by binding to proteins on the viral membranes and clumping into fibrils that entrap the virus and prevent it from entering cells. Further experiments with the transgenic mice revealed that introduction of herpes simplex into the brains of 5- to 6-week-old animals induced rapid development of A-beta plaques, which usually appear only when the animals are 10 to 12 weeks old.

"Our findings show that amyloid entrapment of herpes viruses provides immediate, effective protection from infection," says Moir. "But it's possible that chronic infection with pathogens like herpes that remain present throughout life could lead to sustained and damaging activation of the amyloid-based immune response, triggering the brain inflammation that drives a cascade of pathologies leading to the onset of Alzheimer's disease. A key insight is that it's not direct killing of brain cells by herpes that causes Alzheimer's, rather it's the immune response to the virus that leads to brain-damaging neuroinflammation."

He continues, "Our data and the Mt. Sinai findings suggest that an antimicrobial protection model utilizing both anti-herpes and anti-amyloid drugs, could be effective against early Alzheimer's disease. Later on when neuroinflammation has begun, greater benefit may come from targeting inflammatory molecules. However, it remains unclear whether infection is the disease's root cause. After all, Alzheimer's is a highly heterogeneous disease, so multiple factors may be involved in its development.

Tanzi says, "We are currently conducting what we call the 'Brain Microbiome Project,' to characterize the population of microbes normally found in the brain. The brain used to be considered sterile but it turns out to have a resident population of microbes, some of which may be needed for normal brain health. Our preliminary findings suggest that the brain microbiome is severely disturbed in Alzheimer's disease

and that bad players—including herpes viruses—seem to take advantage of the situation, leading to trouble for the patient. We are exploring whether Alzheimer's pathogenesis parallels the disrupted microbiome models seen in conditions like inflammatory bowel disease, and the data generated to date are both surprising and fascinating."

More information: *Neuron* (2018). [DOI: 10.1016/j.neuron.2018.06.030](https://doi.org/10.1016/j.neuron.2018.06.030)

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