Synthetic peptide can inhibit toxicity, aggregation of protein in Alzheimer's disease

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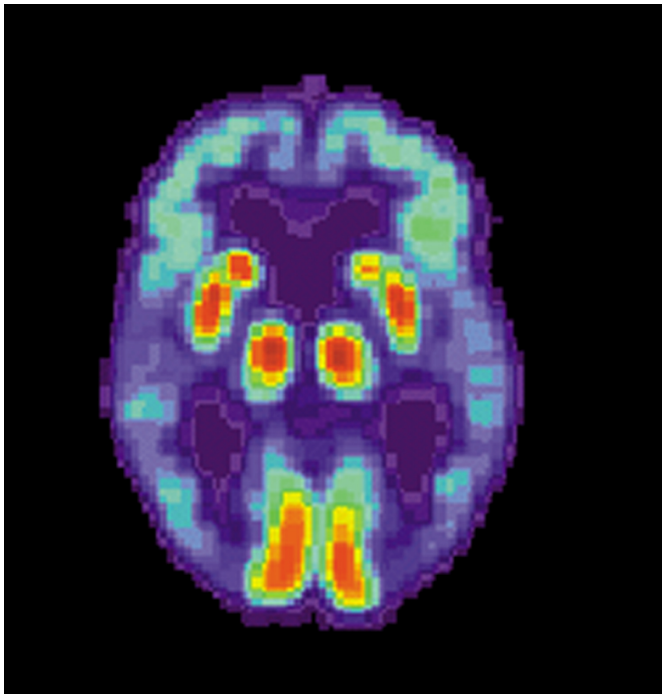

PET scan of a human brain with Alzheimer's disease. Credit: public domain

Alzheimer's is a disease of aggregation. Neurons in the human brain make a protein called amyloid beta. Such proteins on their own, called monomers of amyloid beta, perform important tasks for neurons. But in the brains of people with Alzheimer's disease, amyloid beta monomers have abandoned their jobs and joined together. First, they form oligomers—small clumps of up to a dozen proteins—then longer strands and finally large deposits called plaques. For years, scientists believed that the plaques triggered the cognitive impairments characteristic of Alzheimer's disease. But newer research implicates the smaller aggregates of amyloid beta as the toxic elements of this disease.

Now, a team led by researchers at the University of Washington has developed synthetic peptides that target and inhibit those small, toxic aggregates. As they report in a paper published the week of April 15 in the *Proceedings of the National Academy of Sciences*, their synthetic peptides—which are designed to fold into a structure known as an alpha sheet—can block amyloid beta aggregation at the early and most toxic stage when oligomers form.

The team showed that the synthetic alpha sheet's blocking activity reduced amyloid beta-triggered toxicity in human neural cells grown in culture, and inhibited amyloid beta oligomers in two laboratory animal models for Alzheimer's. These findings add evidence to the growing consensus that amyloid beta oligomers—not plaques—are the toxic agents behind Alzheimer's disease. The results also indicate that synthetic alpha sheets could form the basis of therapeutics to clear toxic oligomers in people, according to corresponding author Valerie Daggett, a UW professor of bioengineering and faculty member in the UW Molecular Engineering & Sciences Institute.

"This is about targeting a specific structure of amyloid beta formed by the toxic oligomers," said Daggett. "What we've shown here is that we can design and build synthetic alpha sheets with complementary structures to inhibit aggregation and toxicity of amyloid beta, while leaving the biologically active monomers intact."

Cellular proteins assume many different 3-D structures, usually by first folding into certain types of basic shapes. The alpha sheet is a nonstandard protein structure, discovered by Daggett's group using computational simulations. The research team has previously shown that alpha sheets are associated with aggregation of amyloid beta. These and related findings indicate that, in nature, alpha

sheets likely occur in only rare instances when proteins fold incorrectly and interact in ways that disrupt cellular function, leading to so-called "protein misfolding" diseases like Alzheimer's.

In this new paper, Daggett and her team provide evidence that amyloid beta oligomers form an alpha sheet structure as they aggregate into longer strands and plaques. Critically, the team's synthetic alpha sheets can actually block this aggregation by specifically binding and neutralizing the toxic oligomers.

Using both novel and conventional spectroscopic techniques, Daggett's team observed the individual stages of development of amyloid beta clusters, from monomers to six- and 12-protein oligomers all the way up to plaques, in human neural cell lines. The researchers confirmed that the oligomer stages were most toxic to the neurons, which agrees with clinical reports of amyloid beta plaques in the brains of people who don't have Alzheimer's.

"Amyloid beta definitely plays a lead role in Alzheimer's disease, but while historically attention has been on the plaques, more and more research instead indicates that amyloid beta oligomers are the toxic agents that disrupt neurons," said Daggett.

In addition, the researchers designed and built small, synthetic alpha sheet peptides, each made up of just 23 amino acids, the building blocks of proteins. The synthetic peptides folded into a hairpin-like structure and are not toxic to cells. But the synthetic alpha sheets neutralized the amyloid beta oligomers in human neural cell cultures, inhibiting further aggregation by blocking parts of the oligomers involved in the formation of larger clumps.

The peptides also protected laboratory animals from toxic oligomer damage. In brain tissue samples from mice, the team observed an up to 82% drop in amyloid beta oligomer levels after treatment with a synthetic alpha sheet peptide. Administering a synthetic alpha sheet to living mice triggered a 40% drop in amyloid beta oligomer levels after 24 hours. In the common laboratory worm Caenorhabditis elegans, another model for Alzheimer's disease, treatment with synthetic alpha sheets delayed the onset of amyloid beta-induced paralysis. In addition, C. elegans worms showed signs of intestinal damage when they were fed bacteria that express amyloid beta. That damage was inhibited when the scientists first treated the bacteria with their synthetic alpha sheets.

Daggett's team is continuing experiments with synthetic alpha sheets to engineer compounds that are even better at clearing amyloid beta oligomers. For the current study, the researchers also created a novel laboratory assay that uses a synthetic alpha sheet to measure levels of amyloid beta oligomers. They believe this assay could form the basis of a clinical test to detect toxic oligomers in people before the onset of Alzheimer's symptoms.

"What we're really after are potential therapeutics against amyloid beta and diagnostic measures to detect toxic oligomers in people," said Daggett. "Those are the next steps."

More information: Dylan Shea el al., "?-Sheet secondary structure in amyloid ?-peptide drives aggregation and toxicity in Alzheimer's disease," *PNAS* (2019). www.pnas.org/cgi/doi/10.1073/pnas.1820585116

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