Researchers determine toxic levels of Alzheimer's clusters in brain

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Scientists have long suspected that Alzheimer's disease (AD) is caused by a small protein called the amyloid β-protein (Aβ). This protein clumps or binds to itself, eventually changing chemically to create brain protein deposits (plaques) that are characteristic of AD. However, recent studies have suggested that it is not the plaques that cause AD but rather these small, grape-like clusters of Aβ. These clusters vary in size, and the relationship between cluster size and their ability to kill nerve cells (toxicity) has never been determined accurately.

Until now. By creating various sizes of Aβ clusters in the lab that exactly match what forms in brains of those afflicted with AD, neurologists at UCLA have determined that toxicity increases dramatically as clusters increase in size from two to three to four Aβs. The researchers also report that although the larger clusters are more toxic than smaller ones, the larger formations are relatively rare; smaller versions are numerous and thus are an inviting target for the development of new therapeutic drugs.

In addition, said David Teplow, senior author and a professor of neurology, developing the ability to make Aβ clusters in a very pure and precise way that duplicates what forms in AD brains will enable scientists to make detailed studies of their structures. This too will make development of future therapeutic drugs much easier and likely more successful. The research appears in the early on line edition of the *Proceedings of the National Academy of Sciences* (PNAS).

Alzheimer's disease is the most common form of late-life dementia. More then five million Americans have been diagnosed with the disease, 24 million worldwide, and the numbers are expected to reach 81 million by the year 2040.

"We now have the best understanding yet of what types of toxic A-beta structures we should target with new classes of therapeutic drugs," said senior author David Teplow, a professor of neurology at UCLA.

The researchers looked at the Aβ molecule, which is the chemical building block for structures that cause Alzheimer's. The molecule binds together, forming clusters of various sizes. The researchers found that the larger the cluster, the greater the toxicity, but they also found that the increase in toxicity with these clusters is not linear.

"Clusters that contain two Aβ molecules are more toxic than a single Aβ molecule, and those with three molecules are more toxic that those with two," said Teplow. But clusters of the Aβ molecule composed of dimers (two Ab molecules forming a cluster) are three-fold more toxic than the simple monomer compound, but trimers (with three Aβ molecules) and tetramers (four molecules) are more than 10-fold more toxic than are monomers, he said.

This suggests that the larger, more toxic clusters should be the target for scientists trying to stop Alzheimer's. But Teplow notes that the relative amounts of the smaller clusters are far greater than that of the bigger clusters and are, in total, more toxic.

So in an Alzheimer's brain, the larger clusters are relatively rare, he said. "Think of the molecules being wrapped in very weak Velcro. So a number of molecules can bind together to form large clusters, but they break apart very easily."

Having developed a process in the lab to be able to make pure forms of these Aβ clusters of specific size will enable detailed study of their structures to show where every atom is. "This will make development of drugs much easier and likely more successful," he said.

Source: University of California - Los Angeles