Novel approach blocks amyloid production in Alzheimer's mouse model

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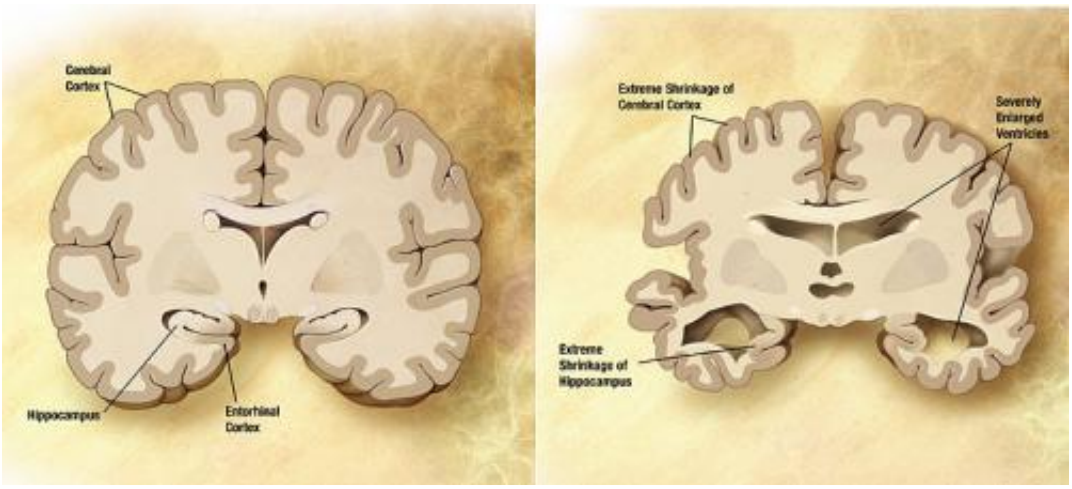

Diagram of the brain of a person with Alzheimer's Disease. Credit: Wikipedia/public domain.

Offering a potential early intervention for Alzheimer's disease (AD), researchers at University of California, San Diego School of Medicine and Cenna Biosciences, Inc. have identified compounds that block the production of beta amyloid peptides in mice. The study is reported April 29 in *PLOS ONE*.

If the results ultimately translate to human treatment, the most promising compound - a peptide dubbed P8 - could be administered to individuals at high risk of developing the disease, long before the tell-tale signs of dementia occur and perhaps with few side effects, due to the

compound's highly specific mode of action.

"Our approach is completely different from any current approaches that target beta amyloid," said lead author Nazneen Dewji, PhD, associate adjunct professor in the Department of Medicine. "We are blocking the actual production of beta amyloid in a new way. It's very promising because it means that, in principle, we can stop the disease in its tracks."

The build-up of beta amyloid plaques is widely believed to cause irreversible brain damage, resulting in a host of cognitive and motor impairments broadly associated with AD, which accounts for about 60 to 80 percent of all cases of dementia in the United States.

Because of the currently perceived role of beta amyloid in disease progression, several investigational drugs have targeted the enzymes that cleave beta amyloid from its larger precursor protein, the aptly named amyloid precursor protein (APP).

"These drugs, however, have largely failed in clinical trials," said Dewji, "mostly because they are responsible for cleaving other proteins besides APP. Inhibiting or modifying their activities creates many undesirable effects in the cell."

The P8 compound does not act on enzymes, but rather binds to APP and in so doing, prevents the larger protein from being processed into smaller amyloid peptides. The compounds are derived from a fragment of a membrane protein known as presenilin 1 that is known to interact with APP to produce beta amyloid. The highly specific binding between the APP and P8 was measured using both biophysical methods and optical imaging techniques.

"Our approach is different, specific and interferes with only the reaction that produces beta amyloid, as opposed to drugs that target the enzymes

responsible for its cleavage from APP, which can affect multiple reactions in cells," said Dewji, who is also president and CEO of the La Jolla-based biopharmaceutical company Cenna, where the drug candidates are being developed.

In addition to cell culture experiments, researchers also conducted experiments with mice, engineered to produce large amounts of the human beta amyloid early in life.

Their experiments showed that a two-week course of treatment with either P8 or another compound called P4 resulted in, on average, a greater than 50 percent reduction in plaque accumulation, as compared with mice who received no treatment.

"We now have a new approach for the treatment of Alzheimer's disease that can arrest the production of beta amyloid very early and specifically," she said. "It's a real chance at a successful treatment for Alzheimer's disease."

Other co-authors include Eliezer Masliah, Edward Rockenstein, Martha Harber, and Taylor Horwood, UC San Diego; and Mihyun Kim, UC San Diego and Cenna Biosciences.

Provided by University of California - San Diego