

Compounds fend off Alzheimer's disease amyloid pathology

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A team of scientists, led by University of California, San Diego School of Medicine researchers, has synthesized hundreds of new compounds with the potential of reducing the production of the A-beta 42 peptide, a primary component of Alzheimer's disease (AD).

In mouse models, one tested compound specifically reduced levels of A-beta 42, which is believed to be responsible for the destruction of neurons, but left other essential enzymatic activities in the brain unaffected, said Steven Wagner, PhD, a project scientist in the UCSD Department of Neurosciences.

The research, which will be published in the September 8 advance online edition of the journal *Neuron*, includes collaborators at the University of Chicago, Memorial Sloan Kettering Cancer Center, Massachusetts General Hospital and several San Diego-based biotechnology companies.

"Current drug efforts have tried to broadly knock out peptide activity, but with resulting adverse side effects such as nausea, gastrointestinal problems, hair color changes and skin cancer," said Wagner. "Our approach is to target and inhibit only the production of key peptides that may play a pivotal role in the pathogenesis of Alzheimer's disease, while leaving other catalytic processes alone. If some of the compounds we've synthesized are shown to do that in humans, we might eventually be able to inhibit or reduce further plaque production and ultimately prevent Alzheimer's before symptoms actually appear."

[Amyloid plaques](#) are tell-tale protein deposits found abundantly in the brains of Alzheimer's patients. The plaques, along with neurofibrillary tangles, interfere with normal neuron functioning. In healthy cellular metabolisms, [chemical compounds](#) are constantly being combined or parsed to perform different duties. Among them are two peptides known as A-beta 42 and A-beta 40. High levels of these peptides, particularly A-beta 42, have been linked to the creation of beta-amyloid plaques in Alzheimer's disease, a neurodegenerative condition that afflicts 5.3 Americans and more than 26 million people worldwide. AD is marked by progressive dementia, most notably memory loss. It is the seventh leading cause of death in the United States.

Existing drugs in development do not specifically target A-beta 42 levels. Wagner and colleagues looked for small molecules that might preferentially reduce levels of A-beta 42, but leave other cellular components and activities alone. The scientists screened more than 80,000 molecules looking for compounds that fit specific criteria. They found one, which they used as a template to synthesize hundreds of additional related compounds called gamma-secretase modulators or GSMs. These compounds are different and far more potent than non-steroidal anti-inflammatory molecules that have been used by others in previous studies. One GSM was tested in a transgenic mouse model designed to overproduce A-beta 42 and 40 and develop neuritic plaques. Given single daily oral doses of the GSM, the researchers report that levels of A-beta 42 declined and neuritic plaques were dramatically reduced in the mouse model.

"We've shown that a compound can modulate enzyme activity without completely shutting down the enzyme," said Wagner. "We think we've opened up a new area of drug discovery for pharmaceutical companies and universities. We hope they will pursue some of these compounds to see if they can be used in people."

Ultimately, said Rudolph Tanzi, PhD, the Joseph P. and Rose F. Kennedy Professor of Neurology at Harvard University and Massachusetts General Hospital and one of the paper's co-authors, the hope is that one or more of the synthesized compounds or something similar might be used to treat, even prevent, [Alzheimer's disease](#).

"They could be used like statins are used today to prevent heart disease," said Tanzi. "If there was pre-symptomatic evidence that amyloid levels were too high in a patient's brain, a GSM might be taken to lower relevant peptide levels and reduce AD risk. You don't want to knock out these peptides. They have a purpose. You just want to dial them back to safe levels."

Provided by University of California - San Diego

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