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New amyloid-reducing compound could be a preventive measure against Alzheimer's

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Scientists at NYU Langone Medical Center have identified a compound, called 2-PMAP, in animal studies that reduced by more than half levels of amyloid proteins in the brain associated with Alzheimer's disease. The researchers hope that someday a treatment based on the molecule could be used to ward off the neurodegenerative disease since it may be safe enough to be taken daily over many years.

"What we want in an Alzheimer's preventive is a drug that modestly lowers amyloid beta and is also safe for long term use," says Martin J. Sadowski, MD, PhD, associate professor of neurology, psychiatry, and biochemistry and molecular pharmacology, who led the research to be published online June 3 in the journal *Annals of Neurology*. "Statin drugs that lower cholesterol appear to have those properties and have made a big impact in preventing coronary artery disease. That's essentially what many of us envision for the future of Alzheimer's medicine."

The 2-PMAP molecule that Dr. Sadowski's team identified is non-toxic in mice, gets easily into the brain, and lowers the production of amyloid beta and associated amyloid deposits.

The prime target for Alzheimer's prevention is amyloid beta. Decades before dementia begins, this small protein accumulates in clumps in the brain. Modestly lowering the production of amyloid beta in late middle age, and thus removing some of the burden from the brain's natural clearance mechanisms, is believed to be a good prevention strategy. Researchers two years ago reported that something like this happens

naturally in about 0.5 percent of Icelanders, due to a mutation they carry that approximately halves amyloid beta production throughout life. These fortunate people show a slower cognitive decline in old age, live longer, and almost never get Alzheimer's.

Prevention of Alzheimer's dementia is now considered more feasible than stopping it after it has begun, when brain damage is already severe. Every prospective Alzheimer's drug in clinical trials has failed even to slow the disease process at that late stage. "The key is to prevent the disease process from going that far," Dr. Sadowski says.

Dr. Sadowski and colleagues screened a library of compounds and found that 2-PMAP reduced the production of amyloid beta's mother protein, known as amyloid precursor protein (APP). The APP protein normally is cut by enzymes in a way that leaves amyloid beta as one of the fragments. Dr. Sadowski's team found that 2-PMAP, even at low, non-toxic concentrations, significantly reduced APP production in test cells, lowering amyloid beta levels by 50 percent or more.

The scientists subsequently found that 2-PMAP had essentially the same impact on APP and amyloid beta in the brains of living mice. The mice were engineered to have the same genetic mutations found in Alzheimer's patients with a hereditary form of the disease, causing overproduction of APP and Alzheimer's-like amyloid deposits. A five-day treatment with 2-PMAP lowered brain levels of APP and, even more so, levels of amyloid beta. Four months of treatment sharply reduced the amyloid deposits and prevented the cognitive deficits that are normally seen in these transgenic mice as they get older.

Dr. Sadowski and his laboratory are now working to make chemical modifications to the compound to improve its effectiveness. But 2-PMAP already seems to have advantages over other amyloid-lowering compounds, he says. One is that it can cross efficiently from the

bloodstream to the brain, and thus doesn't require complex modifications that might compromise its effects on APP.

The compound also appears to have a highly selective effect on APP production, by interfering with the translation of APP's gene transcript into the APP protein itself. The best known candidates for Alzheimer's preventives lower amyloid by inhibiting the secretase enzymes that cleave amyloid beta from APP, tending to cause unwanted side-effects via their off target interference with the processing of other client proteins cleaved by these enzymes. A clinical trial of one secretase inhibitor was halted in 2010 after it was found to worsen dementia and cause a higher incidence of skin cancer.

Alzheimer's disease, the most common form of dementia, currently afflicts more than five million Americans, according to the Alzheimer's Association. Unless preventive drugs or treatments are developed, the prevalence of Alzheimer's is expected to triple by 2050.

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