

Tobacco-derived compound prevents memory loss in Alzheimer's disease mice

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Valentina Echeverria, a researcher at Bay Pines VA Healthcare System and the University of South Florida, was lead author of the cotinine study. Credit: Photo courtesy of Bay Pines VA Healthcare System

Cotinine, a compound derived from tobacco, reduced plaques associated with dementia and prevented memory loss in a mouse model of Alzheimer's disease, a study led by researchers at Bay Pines VA Healthcare System and the University of South Florida found.

The findings are reported online in the *Journal of* <u>Alzheimer's Disease</u> in advance of print publication.

"We found a compound that protects neurons, prevents the progression



of Alzheimer's disease pathology, enhances memory and has been shown to be safe," said Valentina Echeverria, PhD, a scientist at Bay Pines VA Healthcare System and an assistant professor of Molecular Medicine at USF Health. "It looks like cotinine acts on several aspects of Alzheimer's pathology in the <u>mouse model</u>. That, combined with the drug's good safety profile in humans, makes it a very attractive potential therapy for Alzheimer's disease."

While the current drugs for Alzheimer's may help delay the onset of symptoms, none halt or reverse the processes of Alzheimer's disease. In addition, existing drugs may have undesirable side effects.

Some epidemiological studies showed that people who smoke tend to have lower incidences of Parkinson's disease and Alzheimer's disease. Studies have widely attributed this apparently beneficial effect to nicotine, which has been reported to improve memory and reduce Alzheimer's-like plaques in mice. However, nicotine's harmful cardiovascular effects and addictive properties make the compound a less than ideal drug candidate for <u>neurodegenerative diseases</u>.

The Bay Pines VA/USF team decided to look at the effects of cotinine, the major byproduct of nicotine metabolism, in Alzheimer's disease mice. Cotinine is nontoxic and longer lasting than nicotine. Furthermore, its safety has already been demonstrated in human trials evaluating cotinine's potential to relieve tobacco withdrawal symptoms.

The researchers administered cotinine daily for five months to young adult (2-month-old) mice genetically altered to develop memory problems mimicking Alzheimer's disease as they aged. At the end of the five-month study, the Alzheimer's mice treated with cotinine performed better on tasks measuring their working memory and thinking skills than untreated Alzheimer's control mice. Long-term cotinine treatment appeared to provide the Alzheimer's mice complete protection from



spatial memory impairment; their performance in this area of testing was identical to that of normal mice without dementia.

The brains of Alzheimer's mice treated with cotinine showed a 26-percent reduction in deposits of amyloid plaques, which are a hallmark of Alzheimer's disease. Cotinine also inhibited the accumulation of the amyloid peptide oligomers – a predecessor of senile plaques – in the brains of these mice. Furthermore, the researchers discovered that cotinine stimulated the signaling factor Akt, which promotes the survival of neurons and enhances attention and memory.

Senile plaques likely had not yet formed or were just beginning to accumulate in the brains of the young adult mice when long-term cotinine treatment was started. The researchers suggest that "cotinine may be useful in preventing cognitive deterioration when administered to individuals not yet exhibiting Alzheimer's disease cognitive impairment or those with mild cognitive impairment at early stages of the disease."

The researchers are seeking additional support for a pilot clinical trial to investigate cotinine's effectiveness in preventing progression to Alzheimer's dementia in patients with mild cognitive impairment, Echeverria said.

The VA-USF team is also studying the potential of the tobacco-derived compound to relieve fear-induced anxiety and help blunt traumatic memories in mouse models of post-traumatic stress disorder.

More information: "Cotinine Reduces Amyloid-β Aggregation and Improves Memory in Alzheimer's Disease Mice," Valentina Echeverria, Ross Zeitlin, Sarah Burgess, Sagar Patel, Arghya Barman, Garima Thakur, Magorzota Mamcarz, Li Wang, David B. Sattelle, Daniel A. Kirschner, Takashi Mori, Roger M. LeBlanc, Rajeev Prabhakar and



Gary W. Arendash, Journal of Alzheimer's Disease, 24 (4) 2011. DOI:10.3233/JAD-2011-102136, IOS Press.

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