# Inflammatory mediator enhances plaque formation in Alzheimer's disease

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Alzheimer's disease (AD) is a devastating neurodegenerative disorder that causes progressive cognitive impairment and memory loss. Now, a new study published by Cell Press in the September 8 issue of the journal *Neuron* identifies a previously unrecognized link between neuroinflammation and the classical pathological brain changes that are the hallmark of the disease. In addition, the research identifies a new potential therapeutic target for AD.

AD is characterized by abnormal accumulation of amyloid B (AB) protein plaques and neurofibrillary tangles of tau protein in the brain. In addition to these classical hallmarks, neuroinflammation has also been identified as a major component of the disease. Previous research has suggested that AD associated inflammation increases the inducible nitric oxide synthase (NOS2) in neurons and support cells. Importantly, NOS2 leads to generation of nitric oxide (NO) which has been linked with neurodegeneration.

"One of the fingerprints of NO is tyrosine nitration, a posttranslational protein modification that can induce structural changes leading to protein aggregation," explains senior study author, Dr. Michael T. Heneka, from the University of Bonn in Germany. "Since there is so far no mechanistic explanation how expression of NOS2 and the subsequent production of NO and its reaction products modulate AB and thereby the progression of AD, we speculated that nitration of AB might contribute to AD pathology."

In their study, first author Dr. Markus P. Kummer and colleagues discovered that AB is a novel NO target. They observed nitrated AB in AD and AD mouse models and found that this modification accelerated the deposition of human AB. Importantly, reduction of NOS2 reduced AB deposition and memory deficits in a mouse model of AD. Further, nitrated AB induced the formation of amyloid plaques when injected into the brains of mice with genetic mutations associated with AD.

"Taken together, our results identify a novel modification of AB, tyrosine nitration, and propose a causative link between the AB cascade, activation of NOS2, and the subsequent increase in its reaction product nitric oxide during AD," concludes Dr. Heneka. "We think that nitrated AB may serve as marker of early AB plaque formation. More importantly, it may be a promising target for an AD therapy, and that application of specific inhibitors of NOS2 may therefore open a new therapeutic avenue in AD."

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