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Impaired energy metabolism linked with initiation of plaques in Alzheimer's brain

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Scientists have identified an initiating molecular mechanism in sporadic Alzheimer's disease (AD). The study, published by Cell Press in the December 26th issue of the journal *Neuron*, provides new information about generation of damaging amyloid β (Aβ) plaques within the AD brain and underscores the importance of developing new preventative and disease-modifying therapies for AD, especially those aimed at interrupting pathological Aβ-production.

AD, the leading cause of dementia in the elderly, is a devastating neurological disorder characterized by accumulation and deposition of sticky clumps of Aβ protein. Aβ protein is generated from amyloid precursor protein (APP) by β-site APP cleaving enzyme (BACE1). Previous research has suggested that BACE1 activity may play a key role in the initiation of AD pathogenesis and identified BACE1 as a promising target for AD therapeutics.

Recently, BACE1 was linked to cellular stress responses in the brain. Importantly, the AD brain exhibits impaired energy metabolism (a stressful situation) and it has been suggested that diminished cerebral use of glucose and oxygen may be an early event in AD pathogenesis.

Senior study author Dr. Robert Vassar from Northwestern University Feinberg School of Medicine has explored the link between energy inhibition and AD pathogenesis. "We have shown previously, using a pharmacological model of energy metabolism inhibition in pre-plaque transgenic mice with an excess of APP, that BACE1 and Aβ levels are

elevated in the brain," says Dr. Vassar.

Dr. Vassar and colleagues expanded on their previous work by using glucose deprivation to examine the molecular mechanisms underlying elevated BACE1 levels in response to energy inhibition. They found that glucose deprivation caused an increase in BACE1 levels and led to the phosphorylation of the stress-inducible translation initiation factor, eIF2?. Further, direct phosphorylation of eIF2? increased BACE1 levels and enhanced Aβ production while inhibition of eIF2? phosphorylation prevented energy-deprivation induced increases in BACE1.

The researchers went on to show that energy inhibition increased eIF2? phosphorylation, BACE1 levels and amyloid plaque formation in APP transgenic mice. In addition, phosphorylated eIF2? and BACE1 were elevated in an aggressive A? plaque-forming mouse model and in humans with AD.

"Here, for the first time we provide evidence linking impaired energy metabolism, an AD-relevant stress, with BACE1 translation mediated by eIF2? phosphorylation," says Dr. Vassar. "Our findings implicate phosphorylated eIF2? in both the initiation and progression of sporadic AD. Future experiments will determine whether inhibition of eIF2? phosphorylation could be an efficacious therapeutic approach for the prevention and treatment of AD."

Source: Cell Press