Enzyme shreds Alzheimer's protein

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An enzyme found naturally in the brain snips apart the protein that forms the sludge called amyloid plaque that is one of the hallmarks of Alzheimer's disease (AD), researchers have found. They said their findings in mice suggest that the protein, called Cathepsin B (CatB), is a key part of a protective mechanism that may fail in some forms of AD. Also, they said their findings suggest that drugs to enhance CatB activity could break down amyloid deposits, counteracting one of the central pathologies of AD.

Li Gan and colleagues published their findings in the September 21, 2006, issue of the journal *Neuron*, published by Cell Press.

Their experiments were prompted by previous studies showing that the cysteine protease CatB--an enzyme that snips apart proteins--closely associated with the amyloid-ß (Aß) protein that forms the amyloid plaques, a hallmark of AD. However, those studies had not determined whether CatB was "good" or "bad"--that is, whether it acted to produce Aß from a longer protein, called amyloid precursor protein (APP), or whether it broke down Aß.

In their experiments, Gan and colleagues determined that CatB was the latter--breaking down Aß, apparently to enable other enzymes to further degrade the protein for the cell's protein "garbage deposal" system.

They found that knocking out the CatB gene increased plaque deposition in a mouse model of AD in which mice expressed the human form of APP. They also found that CatB tended to accumulate within amyloid

plaques and that it acted to reduce Aß levels in neurons. And they found that introducing a pathological form of Aß, called Aß1-42, into neurons increased CatB in young and middle-aged mice with human APP, but not old mice. "Thus, upregulation of CatB may represent a protective mechanism that fails with aging," wrote the researchers, and such failure may play a role in late-onset sporadic AD.

Their test tube studies showed that CatB biochemically degrades Aß by snipping one end of the protein, called the C-terminal end. What's more, the enzyme also degrades the long strings of Aß that form amyloid plaque, they found.

Finally, they found that increasing levels of CatB in aging mice with human APP markedly reduced plaque deposits in the animals' brains.

Gan and colleagues concluded that "our findings suggest that inhibition or loss of CatB function could interfere with its protective function and promote the development of AD, whereas overexpression of CatB could counteract Aß accumulation and aggregation. Thus, pharmacological activation of CatB could downregulate Aß1-42 assemblies through C-terminal truncation, offering an approach to the treatment of AD."

Source: Cell Press