

THE J. DAVID GLADSTONE INSTITUTES

1650 Owens Street, San Francisco, CA 94158 Telephone: 415.734.2000 www.gladstone.ucsf.edu
in affiliation with the University of California, San Francisco



GLADSTONE INSTITUTE OF NEUROLOGICAL DISEASE NEWS

Contact:

Valerie Tucker
415-734-2019

vtucker@gladstone.ucsf.edu

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GLADSTONE SCIENTISTS IDENTIFY NEW TARGET FOR COMBATING ALZHEIMER'S DISEASE

Modulating enkephalin may reduce cognitive deficits

SAN FRANCISCO, CA – May 7, 2008 ---Alzheimer's disease (AD) is an incurable disease that is increasing in prevalence and will increase even more rapidly as the Baby Boom generation enters the age of highest risk. The available AD drugs are only partially effective in some patients. New strategies are urgently needed.

In a new study, published in today's *Journal of Neuroscience*, researchers in the laboratory of Lennart Mucke, MD, director of the Gladstone Institute of Neurological Disease (GIND), have determined in mouse models that modulating the activity of enkephalin peptides in the brain might reduce the cognitive deficits seen in Alzheimer's disease.

Enkephalins are part of the endogenous opioid system, which modulates learning and memory and other brain functions. They are produced by several different cell types in the brain, particularly in areas affected by AD. Enkephalins are derived by enzymatic cleavage from a precursor protein, preproenkephalin, and stored in vesicles. Upon stimulation, enkephalins are released with neurotransmitters, such as glutamate.

“The enkephalin pathway is an intriguing candidate for us because it is involved in many functions that are affected by Alzheimer's and other neurodegenerative diseases,” said Dr. Mucke. “We were not sure, though, whether it contributed causally to the disease or acts as a compensatory mechanism.”

To better understand the activities of the enkephalins in AD, the Mucke team examined their functions in a transgenic mouse model of AD. These mice express two proteins associated with AD—human

amyloid precursor protein (hAPP) and its cleavage product, A β peptides—in neurons and exhibit several characteristics of AD.

The team found increased levels of preproenkephalin mRNA and of enkephalin in brain regions important for memory that are affected in early stages of AD.

When they genetically manipulated the mice to make them more or less susceptible to neuronal damage, the scientists found that the enkephalin levels were also affected. Furthermore, as levels of the enkephalins increased, the ability of mice to complete behavioral tests declined. Compounds that blocked opioid receptors, through which enkaphalins exert their effects, reduced cognitive deficits. AD patients also showed increased levels of enkephalins in brain regions affected by the disease.

“Our results indicate that the high levels of enkephalins may contribute to cognitive impairments in hAPP mice and maybe also in AD patients,” said Dr. Mucke. “Although these are early results, they are encouraging and may lead the way to a new AD therapy based on limiting enkephalin production or signaling.”

William J. Meilandt , Gui-Qiu Yy, Jeannie Chin Erik D. Roberson, Jorge. J. Palop, Tiffany Wu, and Kimberly Scarce-Levie also contributed to the study. The research was supported by the National Institutes of Health and the Gladstone Institutes.

About the Gladstone Institutes: The J. David Gladstone Institutes, affiliated with the University of California, San Francisco (UCSF), is dedicated to the health and welfare of humankind through research into the causes and prevention of some of the world’s most devastating diseases. Gladstone is comprised of the Gladstone Institute of Cardiovascular Disease, the Gladstone Institute of Virology and Immunology, and the Gladstone Institute of Neurological Disease. More information can be found at www.gladstone.ucsf.edu.

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