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NEW WAYS TO DETECT AND TREAT ALZHEIMER'S DISEASE

Specific brain changes suggest new diagnostic markers and therapeutic targets

SAN DIEGO — New studies identify brain changes in people with Alzheimer's disease. The results give researchers a greater understanding of the disease and may help at-risk individuals by improving early detection. New animal research also shows a novel approach to Alzheimer's vaccine design that may avoid dangerous side effects. These new results were reported at Neuroscience 2010, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news on brain science and health.

About 5.3 million people have Alzheimer's disease, according to the Alzheimer's Association. With the aging baby boomer population, Alzheimer's will continue to affect more people worldwide. Better diagnostic techniques may help identify the disease at earlier, potentially more treatable stages.

Today's new findings show that:
• People with Alzheimer's disease show structural changes in the caudate nucleus, a brain structure typically associated with movement disorders such as Parkinson's disease, suggesting that the disease produces broader damage in the brain than previously thought (Sarah Madsen, abstract 348.4, see attached summary).
• People at risk for Alzheimer's disease exhibit a structural change in portions of the cerebral cortex, which is largely responsible for reasoning, memory and other "higher function" tasks. The findings may help identify those who would most benefit from early intervention (Sarah George, abstract 756.9, see attached summary).
• A new vaccine, which was tested in mice, could protect against memory problems associated with Alzheimer's disease without potentially dangerous side effects. The vaccine targeted a non-human protein that may make it a safer alternative to previous vaccine approaches that caused inflammation in human clinical trials (Charles Glabe, PhD, abstract 725.6, see attached summary).
• Too many small aggregates of a protein called tau in the brain can directly interfere with memory, according to new animal research. The findings are important because they suggest that tau may be a good target for developing therapies against Alzheimer's and related diseases (Ottavio Arancio, MD, PhD, abstract 527.8, see attached summary).

"Identifying those at risk for Alzheimer's and developing new treatments for nervous system disorders is a social imperative," said press conference moderator Sam Sisodia, PhD, of the University of Chicago, an expert on the cellular biology of proteins implicated in Alzheimer's disease. "These studies are evidence that we're making real progress to overcome this tragic epidemic."
This research was supported by national funding agencies, such as the National Institutes of Health, as well as private and philanthropic organizations.

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Abstract 527.8 Summary

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Small Clumps of Tau Protein Disrupt Memory

Animal study suggests possible target for Alzheimer's disease therapies

Too many small aggregates of a protein called tau in the brain can directly interfere with memory, according to new animal research presented at Neuroscience 2010, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.
"Our findings are important because they suggest that tau may be a good target for developing therapies against Alzheimer's and related diseases," said senior author Ottavio Arancio, PhD, of Columbia University.

Many neurodegenerative diseases are marked by an accumulation of protein aggregates in the brain, and Alzheimer's disease is no exception. The two most common aggregating proteins associated with Alzheimer's disease are amyloid-beta and tau, which form the neural plaques and tangles that are hallmarks of the disease. Recently, scientists have begun to focus on some of the smaller, still-soluble forms of these protein aggregates, called oligomers, which may be especially toxic to neurons.
Arancio and his colleagues found that tau oligomers impaired fearful memories in mice. Tau oligomers also disrupted synaptic plasticity — cellular events important for memory formation.

"Our findings suggest that tau is critically involved in the development of Alzheimer's disease — and that reducing the abnormal aggregation of the protein may prove to be an effective treatment approach," Arancio said.

Research was supported by the Alzheimer's Drug Discovery Foundation, the National Institutes of Health, and Oligomerix, Inc.

Scientific Presentation: Tuesday, Nov. 16, 9:45–10 a.m., Room 32B

527.8, Validation of extracellular tau oligomer target for drug discovery in a novel animal model
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TECHNICAL ABSTRACT: Tau protein is found primarily associated with axons in differentiated neurons where it functions to stabilize microtubule structure and regulate transport. However, during Alzheimer's disease (AD) and other tauopathies tau loses its normal function and gains toxic activity. Tau protein aggregates and is sequestered into filaments and higher order neurofibrillary tangles (NFT), a pathological hallmark of AD, and is modified by multiple mechanisms (Ballatore C et al. Nat Rev Neurosci. 2007 8:663-72). Studies using mouse models of AD and tauopathies show a strong correlation between the accumulation of soluble oligomeric species of tau and neuronal loss and memory impairment (Berger Z et al. J Neurosci. 2007 27:3650-62; Brunden KR et al. J Alzheimers Dis. 2008 14:393-9), and have challenged the assumption that NFT are the neurotoxic structures of tau. As AD progresses, tau pathology reproducibly spreads through the hippocampal structure to the cortex in a contiguous, highly selective and orderly fashion (Braak, H. and E. Braak. J Neural Transm Suppl, 1998. 53:127-40; Schönheit B et al. Neurobiol Aging. 2004 25:697-711) suggesting that aberrant tau protein may be involved in transmitting pathology to neighboring neurons during disease progression. Tau pathology may be transmitted to neighboring healthy neurons through muscarinic receptors I and III (Gómez-Ramos A et al. Eur Neuropsychopharmacol. 2009 19:708-17) or by directly entering cells and functioning as a template for intracellular tau to misfold, aggregate and cause neurodegeneration (Clavaguera F et al. Nat Cell Biol. 2009 11:909-13; Frost B et al. J Biol Chem. 2009 284:12845-52). In AD the levels of extracellular tau increase in cerebrospinal fluid, presumably due to release of intracellular proteins during cell death; hence its use as a biomarker for AD (Trojanowski JQ et al. Alzheimers Dement. 2010 6:230-8). Tau secretion to the extracellular space and to postsynaptic neurons was shown to be dependent on the N-terminus of tau and tauopathy mutations facilitating tau aggregation (Kim W et al. J Alzheimers Dis. 2010 19:647-64). Here, we show that extracellular tau oligomers have a causative effect on disrupting memory in studies of synaptic function in hippocampal slices and behavior in mice. Extracellular tau oligomers, but not monomeric tau, reduced long-term potentiation (LTP) (IC50 5 nM) and impaired associative fear memory in normal mice. These results strongly support extracellular tau oligomers as a target for drug discovery for AD and related tauopathies.