



BIOTECH BULLETIN



## Discovery Supports Theory of Alzheimer's Disease as Form of Diabetes

[By Marla Paul]

Insulin, it turns out, may be as important for the mind as it is for the body. Research in the last few years has raised the possibility that Alzheimer's memory loss could be due to a novel third form of diabetes.

Now scientists at Northwestern University have discovered why brain insulin signaling — crucial for memory formation — would stop working in Alzheimer's disease. They have shown that a toxic protein found in the brains of individuals with Alzheimer's removes insulin receptors from nerve cells, rendering those neurons insulin resistant. (The protein, known to attack memory-forming synapses, is called an ADDL for "amyloid  $\beta$ -derived diffusible ligand.")

With other research showing that levels of brain insulin and its related receptors are lower in individuals with Alzheimer's disease, the Northwestern study sheds light on the emerging idea of Alzheimer's being a "type 3" diabetes.

The new findings, published online by the *FASEB Journal*, could help researchers determine which aspects of existing drugs now used to treat diabetic patients may protect neurons from ADDLs and improve insulin signaling in individuals with Alzheimer's. (The *FASEB Journal* is a publication of the Federation of American Societies for Experimental Biology.)

In the brain, insulin and insulin receptors are vital to learning and memory. When insulin binds to a receptor at a synapse, it turns on a mechanism necessary for nerve cells to survive and memories to form. That Alzheimer's disease may in part be caused by insulin resistance in the brain has scientists asking how that process gets initiated.

"We found the binding of ADDLs to synapses somehow prevents insulin receptors from

accumulating at the synapses where they are needed," said William L. Klein, professor of neurobiology and physiology in the Weinberg College of Arts and Sciences, who led the research team. "Instead, they are piling up where they are made, in the cell body, near the nucleus. Insulin cannot reach receptors there. This finding is the first molecular evidence as to why nerve cells should become insulin resistant in Alzheimer's disease."

ADDLs are small, soluble aggregated proteins. The clinical data strongly support a theory in which ADDLs accumulate at the beginning of Alzheimer's disease and block memory function by a process predicted to be reversible.

In earlier research, Klein and colleagues found that ADDLs bind very specifically at synapses, initiating deterioration of synapse function and causing changes in synapse composition and shape. Now Klein and his team have shown that the molecules that make memories at synapses — insulin receptors — are being removed by ADDLs from the surface membrane of nerve cells.

"We think this is a major factor in the memory deficiencies caused by ADDLs in Alzheimer's brains," said Klein, a member of Northwestern's Cognitive Neurology and Alzheimer's Disease Center. "We're dealing with a fundamental new connection between two fields, diabetes and Alzheimer's disease, and the implication is for therapeutics. We want to find ways to make those insulin receptors themselves resistant to the impact of ADDLs. And that might not be so difficult."

Using mature cultures of hippocampal neurons, Klein and his team studied synapses that have been implicated in learning and memory mechanisms. The extremely differentiated neurons can be investigated at the molecular level. The researchers studied the synapses and their insulin receptors before and after ADDLs were introduced.

They discovered that the toxic protein causes a rapid and significant loss of insulin receptors from the surface of neurons, specifically on dendrites to which ADDLs are bound. ADDL binding clearly damages the trafficking of the insulin receptors, preventing them from getting to the synapses. The researchers measured the neuronal response to insulin and found that it was greatly inhibited by ADDLs.

"In addition to finding that neurons with ADDL binding showed a virtual absence of insulin receptors on their dendrites, we also found that dendrites with an abundance of insulin receptors showed no ADDL binding," said co-author Fernanda G. De Felice, a visiting scientist from Federal University of Rio de Janeiro who is working in Klein's lab. "These factors suggest that insulin resistance in the brains of those with Alzheimer's is a response to ADDLs."

"With proper research and development, the drug arsenal for type 2 diabetes, in which individuals become insulin resistant, may be translated to Alzheimer's treatment," said Klein. "I think such drugs could supercede currently available Alzheimer's drugs."



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Klein, Grant A. Krafft, formerly at Northwestern University's Feinberg School of Medicine and now chief scientific officer at Acumen Pharmaceuticals, Inc., and Caleb E. Finch, professor of biological sciences and gerontology at the University of Southern California, reported the discovery of ADDLs in 1998. Krafft is a co-author of the *FASEB Journal* paper. Northwestern and USC hold joint patents on the composition and use of ADDLs in neurodisorders.

The patent rights have been licensed to Acumen Pharmaceuticals, based in South

San Francisco, for the development of drugs that treat Alzheimer's disease and other memory-related disorders.

In addition to Klein, De Felice, and Krafft, other authors on the paper are Wei-Qin Zhao, a former visiting scientist at Northwestern, now with Merck & Co., Inc. (lead author); Hui Chen, from the National Center for Complementary and Alternative Medicine at the National Institutes of Health; Michael Quo, from Blanchette Rockefeller Neurosciences Institute; and Sara Fernandez and Mary Lambert, from Northwestern University.

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Editor's note: William L. Klein is a founder of Acumen Pharmaceuticals, Inc. and serves as a member of its scientific advisory board. In January 2004, Merck & Co., Inc. entered into a research collaboration and license agreement with Acumen to investigate ADDLs as a drug target.

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