Alzheimer's disease: the new promise

Warren J. Strittmatter, MD

Department of Medicine and Department of Neurobiology, Duke University Medical Center, Durham, North Carolina, USA.

Clinical vignette: A 59-year-old aeronautical engineer is referred to you for evaluation because of increasing difficulty with job performance over the last several years. Difficulty managing home finances, getting lost driving, and forgetting appointments have become common. Previously outgoing, he is now depressed and irritable. After appropriate neurologic assessment, including brain imaging and metabolic studies, you make the diagnosis of Alzheimer's dementia and are asked by the patient's family what treatment is available.

Current therapy

Although the disease was first described clinically and pathologically in 1907, clinical care in 2012 is sadly limited to medications that only treat symptoms. Two classes of drugs are FDA approved: acetylcholinesterase inhibitors (donepezil, galantamine, and rivastigmine) and an NMDA receptor antagonist (memantine). Both classes typically produce only minimal and transient symptomatic improvement in memory and well-being. Antidepressant and antipsychotic drugs are sometimes helpful, but several carry black box warnings for use in patients with dementia.

Knowledge gap

In his seminal manuscript, Alzheimer described two microscopic lesions, the extracellular neuritic plaque and the intracellular neurofibrillary tangle (1). The neuritic plaque is formed by β-sheet aggregation of the amyloid-β (Aβ) peptide. Aβ peptide is generated by the proteolytic cleavage of transmembrane amyloid precursor protein (APP) by two proteases, β- and γ-secretase (2). Initial hypotheses of Alzheimer's disease (AD) pathogenesis proposed a central role of the amyloid neuritic plaque in producing dementia. More recent observations, however, demonstrate that small, soluble Aβ oligomers (prior to their self-assembly into the neuritic plaque) directly injure neurons. Unfortunately, small-molecule inhibitors of β- and γ-secretase have failed to demonstrate clinical benefit in randomized clinical trials (3). These recent failures have led to a reappraisal of the strategies in AD drug development (3) and the need to identify additional molecular pathways in AD pathogenesis that might yield better therapeutic targets.

Research advances…

In this issue of the *JCI*, two studies make great strides in revealing a molecular pathway in AD that can be modified by drugs already approved by the FDA for other indications (4, 5). Previous studies have suggested that the molecular pathophysiology of AD significantly overlaps with that of type 2 diabetes and the metabolic syndrome, most notably in insulin resistance. Talbot et al. now demonstrate that insulin resistance in AD occurs not only in peripheral tissues, but also in the brain (4). The authors show that hippocampal brain slices in AD were less responsive to insulin than controls because of increased phosphorylation of IRS-1 that attenuated downstream Akt and ERK signaling. Brain insulin resistance in AD was not dependent on diabetes, or on the *APOE4* genotype, which also affects the Akt pathway (6) and is a major determinant of risk for non-Mendelian AD.

Demonstrating insulin resistance in the AD brain has therapeutic implications, since this pathway can be modified by FDA-approved insulin-sensitizing drugs: metformin, the glucagon-like peptide–1 (GLP-1) mimetics exenatide and liraglutide, and PPARγ agonists. Also in this issue, Bomfim et al. demonstrate a critical role of the soluble Aβ oligomer in producing brain insulin resistance in AD and successfully demonstrate pharmacologic manipulation of this pathway by a GLP-1 agonist (5). Using multiple model systems, the authors show that soluble Aβ oligomers increased the production of the inflammatory cytokine TNF-α, leading to phosphorylation of IRS-1 by JNK. Moreover, a small-molecule activator of the GLP-1 receptor, developed to treat type 2 diabetes, reduced the phosphorylation of IRS-1 in the brain and improved cognition in a mouse model of AD.

Additional support for the pharmacologic enhancement of insulin signaling to treat AD comes from other investigators who have shown that nasally inhaled insulin improved clinical outcomes in small trials (7).

Recommendations

Dementia is defined as a gradual decline of cognitive skills sufficiently severe that the patient has difficulty with activities of daily living. Patients and families are typically overwhelmed when the diagnosis is first mentioned. While I prescribe the FDA-approved drugs mentioned above, it is important to emphasize the critical role played by advocacy groups, such as the Alzheimer's Association, social workers, and multidisciplinary clinics, in the care of these patients. Structured education helps inform the family about the increasing needs for safety supervision, daily care, and establishing legal guardianship for financial and health decisions. The studies highlighted above suggest a path forward in the development of new therapies for AD by targeting the IRS-1/Akt pathway and may soon provide hope to patients with this devastating disease.

Address correspondence to: Warren J. Strittmatter, Duke University Medical Center, Bryan Research Bldg., Room 227, Durham, North Carolina 27710, USA. Phone: 919.684.6274; Fax: 919.684.6514; E-mail: warren@neuro.duke.edu.

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