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GUEST EDITORIAL

Genetic discoveries as the basis of personalized therapy: rosiglitazone treatment of Alzheimer's disease

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Alzheimer's disease (AD), a progressive neural degeneration leading to deterioration in memory and comprehension, is increasing in prevalence as the elderly population grows in number. Few treatments are available for this highly morbid condition, but as more pathologic mechanisms are uncovered, targeted therapies can be developed. Thus, the paper by Risner *et al*. (pages 246–254) is intriguing because of a potential new strategy in the treatment and possible prevention of AD. This multicenter, interventional study randomized 518 subjects (50–85 years old) with mild to moderate AD to placebo, 2, 4, and 8 mg daily of rosiglitazone administration for 6 months. The two pre-specified primary end points were change from baseline to week 24 in the ADAS-Cog and C1B1C – Plus global score. No differences were seen in the primary end points between placebo and any dose of rosiglitazone. However, subjects who were apolipoprotein E ε4 (APOE ε4) negative did show improvement in ADAS-Cog at the 8 mg rosiglitazone dose. APOE ε4-positive patients showed no improvement and even some decline on rosiglitazone. The authors suggested that improving insulin sensitivity may improve brain glucose utilization, which is reportedly defective in AD.[1] They noted that insulin resistance and diabetes may predispose to AD.[2] In this study, APOE ε4-negative subjects had a greater drop in fasting insulin in response to rosiglitazone compared to APOE ε4-negative subjects. In a smaller preliminary study, Watson *et al*.[3] randomized 30 subjects with mild AD or amnestic mild cognitive impairment to 6 months of rosiglitazone (4 mg daily) or placebo. The rosiglitazone group had better delayed recall and selective attention, as well as stable plasma amyloid beta (Aβ) levels, which declined in the placebo group (declining plasma Aβ levels may suggest progression of AD). Clearly, further studies are needed to assess the efficacy of rosiglitazone in AD and to determine whether rosiglitazone enhances brain glucose uptake and whether this correlates with clinical improvement.

Insulin has been implicated in the pathogenesis of AD. In elderly subjects, hyperinsulinemia is a risk factor for AD and decline in memory.[4] Insulin infusion into healthy, older subjects, increases cerebral spinal fluid (CSF), insulin levels as well as CSF Aβ levels.[5,6] In rodents, insulin is related to insulin receptors and insulin-dependent glucose transports have been identified in brain areas controlling memory.[7] Memory training increases insulin receptor message levels in certain areas of the brain, such as the hippocampus.[7] Whether insulin resistance alters memory function is unknown. In addition, insulin facilitates release of Aβ from intraneuronal compartments and interferes with its degradation. This effect has been shown to attenuate memory.[8] Rosiglitazone treatment improves insulin resistance, thereby lowering circulating insulin levels. It is possible that this effect may contribute to the results seen in the present study.

Other mechanisms of action of rosiglitazone in AD, however, need to be considered in order to optimize therapeutic efficacy. Rosiglitazone is a ligand to the nuclear receptor, peroxisome proliferator-activated receptor γ, PPARγ.[9] This receptor is abundantly expressed in adipose tissue, but is also present in a variety of other tissues including liver, vasculature, heart, brain, kidney, skeletal muscle, monocytes, bone marrow and others. It is approved as an oral hypoglycemic agent for use in type II diabetes mellitus. Studies of tissue-specific PPARγ knockout mice have helped to delineate its mechanism of action in glucose transport. Activation of PPARγ decreases plasma glucose by (1) directly enhancing insulin-mediated glucose uptake in skeletal muscle,[10] (2) directly suppressing hepatic glucose production[11] and (3) indirectly by transcriptional upregulation of adiponectin expression in adipose tissue.[12] Adiponectin enhances insulin-mediated glucose uptake into skeletal muscle and suppresses hepatic glucose production by activating the cyclic-3′,5′-adenosine monophopshate-kinase pathway through binding to adiponectin R1 receptors primarily in skeletal muscle and R2 receptors in liver.[13,14] Brain glucose uptake is not insulin-dependent, so it is not clear that peripheral insulin resistance in skeletal muscle and liver would be associated with defective brain glucose uptake. However, it is possible that adiponectin could impact on brain glucose transport as R1 receptors are present in the brain.[14] Adiponectin also has profound anti-inflammatory effects that could attenuate the cerebral inflammation that occurs in AD.

Another potentially exciting mechanism amyloid precursor protein (APP), abnormal processing of the transmembrane protein, APP, appears to occur in the early onset forms of AD with increased synthesis of β-amyloid and/or decreased clearance leading to increased deposition, toxicity and apoptosis of neuronal cells.[15,16] Indeed, mutations in the APP gene and in the presenilin 1 and 2 genes are associated with increased brain APP and are present in 50% of autosomal-dominant forms of early-onset AD.[17,18] In contrast, the APOE ε4 mutation is more commonly associated with late-onset AD/out APOE was also found to be involved in amyloid plaques in a mouse model.[19] Exactly how these plaques produce brain injury is unclear. Nevertheless, early identification of β-amyloid fibrils in temporal and other areas of the brain using nuclear magnetic resonance imaging appears predictive of the development and progression of AD.[20] In patients with type II diabetes mellitus, another variant of the amyloid protein, amyloid-associated protein (AAP) accumulation in the islet cells of the pancreas and in conjunction with other toxic factors, including fatty acids, inflammatory mediators and oxidative stress induce islet cell apoptosis.[21–24] We reported that rosiglitazone prevents AAP-induced apoptosis of cultural human islet cells by activating the phosphoinositol 3-kinase pathway and preventing upregulation of proapoptotic genes.[24] An attractive hypothesis is that rosiglitazone may be protecting the brain from APP by similar antiapoptotic mechanisms. Perhaps, common abnormalities associated with the accumulation of amyloid-associated proteins explains, at least in part, the prevalence of AD in patients with diabetes.

Vascular injury could also explain the relationship between diabetes and AD. Both small and large vessels are damaged in diabetes leading to accelerated atherosclerosis and microvascular complications. Damage to brain vessels may increase susceptibility to β-amyloid-induced injury and accentuate symptomology. PPARγ ligands have anti-inflammatory and antioxidant properties that appear to protect the vasculature. They may delay cardiovascular disease[25] and may attenuate diabetes microvascular complications.[26–28] Protecting blood vessels by lowering cholesterol and treating hypertension is, indeed, recommended for patients with AD.[29] The anti-inflammatory and antioxidant actions of rosiglitazone may also protect brain tissue in AD in addition to blood vessels.

The fact that the PPARγ ligand rosiglitazone may improve AD by several mechanisms underscores the need for further investigations of ligand effects in cells and animal models and for further clinical trials. PPARγ is expressed in a wide variety of tissues and has diverse actions. If its effects in AD could be defined, more specific receptor modulators could be developed for AD.

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