Insulin Sensitizers Cut Cognitive Decline in AD

BY ROBERT FINN
San Francisco Bureau

SAN FRANCISCO — A growing body of evidence suggests that insulin sensitizers may avert cognitive decline in people with Alzheimer's disease, Suzanne Craft, Ph.D., said at the Third World Congress on Insulin Resistance Syndrome.

In one randomized, placebo-controlled clinical trial, rosiglitazone appeared to be effective in preserving memory and selective attention in a small group of patients with early Alzheimer's disease (AD) or mild cognitive impairment (MCI), said Dr. Craft of the University of Washington, Seattle.

Another randomized trial involved elderly patients with impaired glucose tolerance (IGT) or type 2 diabetes mellitus (T2DM) and contained three arms: placebo, pioglitazone, and nateglinide. Both pioglitazone and nateglinide improve glucose tolerance, but only pioglitazone improved insulin sensitivity and reduced insulin levels. In this trial, pioglitazone, but not nateglinide or placebo, improved performance in a memory test.

"If you pick up an endocrinology textbook from about 15 years ago, you may very well read that 'the brain is an insulin-insensitive organ,' " Dr. Craft said. "We're coming to understand that's very much not the case. There is a critical relationship between insulin resistance and key aspects of brain function."

In fact, the brain contains many insulin receptors, which tend to be clustered in the hypothalamus, where insulin likely helps regulate eating behavior, and in cortical regions closely linked to cognition.

In earlier studies on healthy individuals Dr. Craft and her colleagues determined that experimentally induced hyperinsulinemia increases the production of the 42-peptide form of β-amyloid (Aβ), the precursor of the amyloid plaques that are the hallmarks of AD. The relationship between insulin levels and Aβ turned out to be age related, and was especially apparent in people over the age of 70.

On a story recall test, improvement among patients who were taking pioglitazone was proportional to the extent of their metabolic treatment response.

The rosiglitazone trial compared 20 patients taking 4 mg of the drug daily for 6 months with 10 patients taking placebo. All of the patients had a confirmed diagnosis of AD or MCI and averaged 73 years of age. Patients taking rosiglitazone did have significantly lower fasting plasma insulin levels than control patients, but there were no differences between the groups on fasting glucose, lipids, or liver enzymes (Am. J. Geriatr. Psychiatry 2005;13:950-8).

At 4 and 6 months into the study, patients taking rosiglitazone performed significantly better than those taking placebo on a delayed memory task (the Buschke Selective Reminding Test). At the 6-month time point patients taking rosiglitazone performed significantly better on a measure of selective attention (the Stroop Color-Word Test).

The other trial, which has not yet been published, involved 71 patients over the age of 55 with IGT or T2DM. Patients were randomly assigned to receive placebo, pioglitazone (30 mg/day), or nateglinide (360 mg/day) for 4 months.

Compared with baseline, patients taking pioglitazone showed significant improvement in performance on a story recall test, while patients taking nateglinide or placebo showed no such improvement. Furthermore, among the patients taking pioglitazone, the improvement was directly proportional to the extent of their metabolic treatment response, as measured by a 2-hour oral glucose tolerance test.

A subset of these patients received PET scans at baseline and after 4 months of treatment. As expected, insulin-resistant patients showed hypometabolism in the left temporal lobe and the right parietal region, both areas that are known to be affected in the very early stages of AD.

In addition, while performing a task of word memory in the PET scanner, normal subjects showed a pattern of increased glucose metabolism in the right frontal lobe. Patients with IGT showed a significantly smaller increase in glucose metabolism in that area, and patients with T2DM showed a smaller increase still.

Pioglitazone and rosiglitazone were both tolerated well in the two trials.

Although these studies are small and preliminary, if confirmed in larger studies, they open the possibility that insulin sensitizers may provide an effective treatment for the cognitive decline seen in Alzheimer's disease. ■

Pathology Shows Amnestic MCI Is Same Entity as Early Alzheimer's

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

Amnestic mild cognitive impairment is neuropathologically the same entity as early Alzheimer's disease and represents a transition from the normal aging brain to the profound pathology of Alzheimer's, according to Dr. William Markesberry and colleagues.

The transition appears to be marked more by an increase in neurofibrillatory tangles than in dendritic or neuritic plaques, wrote Dr. Markesberry of the University of Kentucky, Lexington, and his associates.

The researchers followed 43 elderly subjects who were cognitively normal at baseline, until their deaths: 23 of them remained cognitively normal, 10 developed amnestic MCI, and 10 developed early Alzheimer's disease (EAD).

All of the brains were available for autopsy via prior arrangement with the subjects (Arch. Neurol. 2006;63:38-46).

Comparison of the brains from patients with EAD to normal brains found significant increases in all the pathologic hallmarks of the disease (dendritic plaques, neuritic plaques, and neurofibrillatory tangles) in all of the neocortical and ventromedial regions.

There were no significant differences in the number of dendritic plaques between the controls and those with MCI, nor between the MCI brains and the EAD brains. "Because dendritic plaques were so common in normal control subjects, our data suggest that they are not critical neuropathologic determinants of the transition from normal to MCI, or MCI to EAD," the investigators wrote.

Neuritic plaques were significantly more common in the MCI brains than in the control brains. But when the MCI brains were compared with EAD brains, the plaques only increased significantly in the amygdala and subiculum.

"This indicates that the pathologic deposition of insoluble β-amyloid peptide and formation of neurites in the cerebral cortex progress from normal to MCI, but in contrast, they do not distinguish MCI from EAD."

The most striking difference between the brains was the amount of neurofibrillatory tangling. Compared with normal brains, the MCI brains showed significantly more tangles in the inferior parietal lobule, amygdala, entorhinal cortex, and subiculum. When compared with MCI brains, EAD brains showed an expansion of the tangles, with significantly more in the middle temporal gyrus, middle temporal gyrus, amygdala, and subiculum.

These changes imply neuropathologic progression, the researchers wrote. "The increase in [tangles] in all of the neocortical and ventromedial lobe structures in EAD, compared with controls, further supports a gradual increase in [tangle] formation from normal aging to having MCI to having EAD."

The conclusions argue for a change in the diagnostic criteria of early Alzheimer's and MCI, Dr. John Morris wrote in an accompanying editorial.

The standard criteria, which were developed years ago, can't distinguish between the mild stages of Alzheimer's and MCI that are now identifiable, wrote Dr. Morris of Washington University, St. Louis (Arch. Neurol. 2006;63:15-6).

"Revised criteria should permit the diagnosis of AD at these early stages, because … AD pathology is already established. Moreover, the earliest stages of AD may be the optimal time for interventions with drugs now in development that have the potential to retard or even arrest the AD process." ■

Atrophy of Hippocampus and Amygdala Linked to Dementia

BY MARTHA KERR
Contributing Writer

Hippocampal and amygdalar atrophy are predictive of dementia in the cognitively intact elderly, Dutch researchers reported.

The investigators studied 511 community residents aged 60-90 years and free of dementia at baseline. The objective of the study, conducted by Dr. Tom den Heijer of Erasmus Medical Center in Rotterdam, the Netherlands, and his colleagues, was to assess whether atrophy of the hippocampus and amygdala was present before the onset of dementia. All of the participants were part of The Rotterdam Study, a prospective, population-based study launched in 1990.

In the current investigation, volumetric assessment of the hippocampus and amygdala was evaluated by MRI. The investigators also performed extensive neuropsychological testing and questioned participants about daily memory problems (Arch. Gen. Psychiatry 2006;63:57-62).

During a mean follow-up of 6 years, 35 of the participants developed dementia, 26 of whom were diagnosed with Alzheimer's disease. The investigators found that those participants who developed dementia had much smaller hippocampal and amygdalar volumes at baseline than did those without incident dementia.

Furthermore, they found that volume reduction at baseline was inversely associated with time until the onset of dementia. This was true "even in persons without memory complaints or low cognitive performance at baseline," the investigators reported.

Dr. den Heijer and his colleagues said that MRI findings have been validated by previous autopsy studies of brain tissue showing neuronal loss and Alzheimer's disease.

Decreases in hippocampal and amygdalar volumes of 5%-17% were found, depending on how far in advance of dementia the MRI was done. For individuals with Alzheimer's disease, Dr. den Heijer's team found reductions ranging from 25% to 40%, a range that suggests that the atrophy rate accelerates in patients with Alzheimer's disease.

The investigators concluded that "structural imaging can help identify people at high risk for developing dementia, even before they have any memory complaints or measurable cognitive impairment." They hastened to add, however, that most people with atrophy failed to develop dementia, even after 6 years. ■

Pages 42a—42h