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 Syndromes.

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 13 years ago, you may very well read that ‘the brain is an insulinsensitive 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 certain aspects of brain function.”

One of the main conclusions of the studies may be that higher insulin and insulin-related factors may provide a protective effect, even in patients without diabetes.

However, patients taking pioglitazone showed improvements on a delayed recall test, compared with baseline and also with those taking placebo. Patients taking rosiglitazone showed similar improvements in this cognitive domain.

“We have seen patients act better on memory tests when insulin levels are lower, and we think it’s because insulin has a critical role in the brain,” Dr. Craft said. “But we don’t think it’s a direct role.”

While patients taking pioglitazone or placebo showed no change in cognitive performance, the patients taking rosiglitazone showed an increase in performance in a delayed recall test.

Although Alzheimer’s disease is a complex and multifaceted condition, Dr. Craft and her colleagues determined that rosiglitazone may improve cognitive function in early Alzheimer’s disease, and that this may be due to its insulin sensitizing effects.

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

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

A mnestic mild cognitive impairment is neuropathologically and clinically the same entity as early Alzheimer’s disease and represents a transition from the normal brain aging 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 neurofibrillary 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;63:18-46). Comparison of the brains from patients with EAD to normal brains found significant increase in pathologic hallmarks of the disease (dendritic plaques, neuritic plaques, and neurofibrillary 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 somewhat 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 process in amyloid beta amyloid peptide formation of neuritic plaques is not an early event relative to normal aging in AD, but that it does not distinguish MCI from EAD,” the investigators wrote.

The most striking difference between the brains was the amount of neurofibrillary tangles. Compared with normal controls, the MCI brains showed significant increase in tangles in the inferior parietal lobe, 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 neuropsychologic progression, the researchers wrote. “The increase in [tangles] in all of the neocortical and ventromedial lobe structures in EAD, compared with controls, further suggests 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, cannot distinguish between the mild stages of Alzheimer’s and MCI that are now identifiable, wrote Dr. Morris of Washing ton University, St. Louis (Arch. Neurol. 2006;63:13-16).

“Revised criteria should permit the diagnosis of AD at these early stages, because there is already established pathology, even if it is not the case. Moreover, the earliest stages of AD may be the optimal time for intervention 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

H hipocampal 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 1%-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 have tested this finding, however, that most people with atrophy failed to develop dementia, even after 6 years.