Madrid: Highs and Lows of The Insulin Connection

14 September 2006. Frequently in Alzheimer research, new trends take form when epidemiologic studies suggest an association between the risk of developing Alzheimer disease and some second factor. One such area that is growing in strength is the overlap between type 2 diabetes and Alzheimer disease. More broadly, all components of what is loosely called metabolic syndrome—hypertension, high blood lipids, high blood sugar, insulin resistance, obesity—are linked with increased risk for age-related dementia. While mechanistic studies are ongoing and the epidemiologic connection is still growing in strength, some groups are already beginning to report results of some initial clinical trials (see below). Unfortunately, also frequently in AD research, tantalizing hints of a therapeutic effect show up in small pilot trials, only to fall flat when tested subsequently in larger, better-controlled studies. One problem is that, sometimes, trials are designed without sufficient input from basic scientists before underlying biologic processes of the new association, and specific biologic markers for it, are worked out for clinical trials to measure. The insulin/diabetes connection so far is no different.

One pilot trial reported at ICAD tested insulin itself. The underlying rationale is that plasma hyperinsulinemia and insulin resistance in the periphery paradoxically lead to a deficiency of insulin in the brain, probably because the peripheral condition changes the receptor-mediated transport of insulin at cells of the blood-brain barrier. Addressing this issue, **Suzanne Craft** and colleagues at the University of Washington, Seattle, attempted to deliver insulin directly to the brain by way of the nose. This route might be able to avoid the low blood sugar that would result from systemic insulin treatment (see also Born et al., 2002). The scientists used electronic atomizers to spray insulin into the noses of people with early AD or amnestic MCI for 3 weeks. Of 25 patients, 13 were randomized to receive 20 international units of insulin daily and 12 to placebo. Plasma glucose and insulin levels happily did not change in insulin sniffers, nor did they suffer other side effects, Craft reported. The placebo and insulin group performed equally on verbal recall tests at baseline, but at the end of the trial the insulin group outperformed the placebo group. Older patients responded less well than younger patients. Intriguingly, intranasal insulin appeared to change plasma Aβ and cortisol levels.

Instead of using insulin, perhaps current type 2 diabetes drugs might work for AD? After all, AD is sometimes called "type 3 diabetes," and some widely used drugs effectively increase the body's sensitivity to insulin and lower blood glucose levels. GlaxoSmithKline's rosiglitazone and Takeda Pharmaceutical/Lilly's pioglitazone both are thiazolidinedione compounds that act as agonists of the PPARγ nuclear receptors. First, consider rosiglitazone. A small trial by Craft and colleagues had suggested a cognitive benefit in AD patients (Watson et al., 2005), and in Madrid, scientists from GlaxoSmithKline presented data for a large follow-up study. In a 6-month double-blind, placebo-controlled, dose-ranging trial of an extended-release form of rosiglitazone in 518 non-diabetic AD patients, the drug showed a similar safety profile as was previously established for diabetic patients. Edema and cardiac complications occurred as anticipated (see also ARF related news story), but no additional side effects cropped up in

this AD population. The trial at first looked good: the patients were newly diagnosed, did not also take cholinesterase inhibitors or memantine, and 85 percent completed the trial. Unfortunately, the drug did not significantly improve their ADAS-Cog or CIBIC scores, reported **Marina Zvartau-Hind** of GlaxoSmithKline in Greenford, United Kingdom. There was no significant difference between the rosiglitazone and the placebo group. (The placebo group barely declined, as sometimes happens in 6-month trials of this slow-moving disease.)

This disappointing result could have ended the effort. Yet when the investigators analyzed, as planned, the ApoE4-positive and negative trial participants separately, they found a ray of hope. Patients without an E4 allele had, in fact, improved on the highest dose given, whereas people with one ApoE4 allele showed no benefit, and people with two ApoE4 alleles declined (Risner et al., 2006). Subgroup analysis is weaker than the result on the primary endpoint. Zvartau-Hind noted that this exploratory finding can't help a doctor decide whether to prescribe rosiglitazone to a given AD patient. It also is not sufficient to encourage patients to find out their ApoE status. But the finding has swayed GlaxoSmithKline to continue testing rosiglitazone for AD, and larger trials powered to study its effect both in ApoE4 carriers and non-carriers are planned.

Rosiglitazone's competitor pioglitazone also was put to the test, though a smaller one. **David Geldmacher** of the University of Virginia, Charlottesville, with colleagues at University Hospitals and Case Western Reserve University in Cleveland, Ohio, reported results of their 18-month trial of this drug in 29 non-diabetic AD patients. They were randomized to take either the drug or placebo but unlike in the GlaxoSmithKline trial, also took cholinesterase inhibitors and/or memantine. More than a quarter of the people in the treatment group developed edema; otherwise, they tolerated the drug well. Cognition, function, and behavior did not improve significantly, but there was a positive trend that the investigators interpret to warrant a larger trial on this drug, as well.

If those drugs are no home run, how about going after the signal transduction cascade downstream of insulin, to boost the hormone's downstream effects? The literature is ripe with evidence implicating reduced levels of insulin-like growth factor-1 (IGF-1) in aging, cognitive decline, AD, and amyloid degradation (e.g., Rivera et al., 2005; for a recent review, see Messier and Teutenberg, 2005). Led by **J. Michael Ryan**, scientists at Merck Research Laboratories in North Wales, Pennsylvania, took a cue from that body of work and tested MK-0677, a compound that induces secretion of IGF-1. They randomized 563 AD patients with baseline MMSE scores between 14 and 26 to take either MK-0677 or placebo daily for a year. In this double-blind trial, MK-0677 did increase IGF-1 serum levels by 60 percent. Sadly, this failed to move any of the clinical treatment endpoints. Both CIBIC-plus and ADAS-Cog scales showed little change; neither did secondary endpoints.

What gives? Does the failure of large trials mean the epidemiological data are wrong? No, scientists across the field generally agree. Epidemiologists cautioned that one possible reason why trials have shown little effect is that epidemiology data are converging to show a link between components of the diabetic syndrome in mid-life and

elevated risk for AD a decade or two later. As happened with anti-inflammatory drugs and estrogen, the trials tested drugs that are based on a mid-life risk factor in the hope that the drug will still be able to help a much older brain that has since degenerated considerably. To design better intervention—or even prevention—trials in younger people, more mechanistic insight in the underlying processes of metabolic syndrome components in AD is needed. This is particularly urgent because most patients have mixed forms of AD and vascular dementia, said **Monique Breteler** of Erasmus University in Rotterdam, The Netherlands. Echoing a similar story for estrogen, **Kristin Yaffe** of University of California, San Francisco, noted that after the disheartening failure of conjugated horse estrogen in the Women's Health study, researchers have tried to focus on a critical period of dementia initiation in late mid-life, when endogenous sex hormone levels decline. They are beginning to test designer estrogens such as raloxifene for their ability to protect against MCI, not dementia (Yaffe et al., 2005).

The association between a history of diabetes and risk for AD is undisputed, but the mechanisms are nebulous, agreed **Richard Mayeux** of Columbia University, New York. Leads for possible mechanisms include insulin's role in Aβ clearance by competition for the enzyme IDE, its downregulation of the tau kinase GSK3β, and its effect on the neuroprotective Akt signaling pathway. Does insulin resistance change the outcome of these pathways toward AD? Insulin-resistant adults have lower CSF Aβ42 levels, which other work has suggested foreshadows future AD. Research should focus on how increased CSF insulin might damage the brain's microvasculature and blood-brain barrier and, in turn, lower insulin signaling inside the brain. More broadly, mechanisms accounting for microvascular damage could explain some of the established overlap between vascular dementia and AD. The focus in this area is slowly shifting away from ischemia and toward small hemorrhages and vascular amyloid, noted Breteler.

Research also should focus on a clear delineation between the effect of central insulin on Aβ and peripheral insulin on Aβ. If blood insulin levels increase peripheral Aβ, especially large amounts produced in muscle, then the direction of transport could shift toward Aβ import into the brain. Insulin is one of several factors that affect APP metabolism, Mayeux added, all of which deserve a clear description of the mechanistic pathway. Examples include dietary factors and stress. Hormones released by fat in that dangerous potbelly, as well as elevated glucocorticoids, cause insulin resistance and can lead to the same functional hypoglycemia in the brain that is seen in diabetes (see also Green et al., 2006; see ARF Madrid story). Understanding these mechanisms could pay off not only in better trial design but also in early detection and, eventually, prevention. The scientists agreed that epidemiology and basic science need to move in concert toward this goal.

A final note on the anti-inflammatory treatment front, which has suffered from similar problems. A trial of triflusal, an antithrombotic drug that also appears to inhibit NF-κB in the brain, showed a hint of promise toward reducing progression from MCI to AD in 257 people. However, slow recruitment forced a premature end to this trial, led by **Teresa Gomez-Isla** of the Hospital Santa Creu i Sant Pau in Barcelona, Spain, and conducted there and in Lisbon, Spain. An Italian trial of ibuprofen, conducted by researchers in Brescia, Pavia, Turin, and Rome, failed to slow cognitive decline in patients with mild-

to-moderate AD in 132 patients. A longer-term follow-up of R-flurbiprofen confirmed and extended a moderate positive effect on cognition in patients with mild AD reported earlier (see ARF related conference story).—Gabrielle Strobel.