Diabetes, Dementia, and Alzheimer's Disease

Diabetes Mellitus Interagency Coordinating Committee (DMICC) Meeting of August 16, 2012

The goal of this meeting was for DMICC members to learn more about the evidence linking diabetes with dementia and Alzheimer's disease (AD), and to discuss DMICC member agency activities relevant to this problem. The general increase in diabetes prevalence combined with a rapidly aging U.S. population makes this interrelationship an important public health challenge. Understanding the interrelationship between these diseases could potentially yield new approaches for treatment and strategies for prevention.

Diabetes and Dementia: Untangling the Web —Dr. Suzanne Craft, University of Washington School of Medicine

Dr. Craft is Professor of Psychiatry and Behavioral Sciences at the University of Washington; she is also Associate Director of the Geriatric Research, Education, and Clinical Center, and Director of the Memory Disorders Clinic, at the VA Puget Sound Medical Center. With support from the NIH, the VA, and other sources, Dr. Craft has focused her research program on neuroendocrine abnormalities in the development and expression of AD. AD is an irreversible, progressive brain disease that slowly destroys memory and thinking skills, and eventually even the ability to carry out the simplest tasks. AD is the most common cause of dementia among older people, and prevalence increases exponentially with age. While estimates vary, experts suggest that several million Americans may have AD. Dr. Craft noted epidemiological studies finding that insulin resistance, hyperinsulinemia, and impaired glucose tolerance (IGT)/type 2 diabetes are associated with increased risk for cognitive impairment and AD; these observations are consistent with evidence showing that insulin normally plays a positive role in brain function and cognition. As a result, Dr. Craft and other researchers are investigating biological mechanisms that could be responsible for the increased risk for diminished brain function associated with prediabetes and diabetes.

The brain's primary energy source is the sugar glucose. Through imaging studies of people with preclinical AD, Dr. Craft and colleagues have observed patterns of impaired glucose metabolism in the brain that can be detected well before clinical onset of the disease. Conversely, they have observed that patterns virtually identical to the AD risk patterns can be found in cognitively normal people with prediabetes and type 2 diabetes, a resemblance that increases with increasing levels of insulin resistance.

Delving into the potential molecular mechanisms linking development of cognitive impairment with dysfunctional glucose metabolism in the brain, Dr. Craft and her colleagues examined the interplay between insulin, insulin resistance, and beta amyloid, also called A-β—the key component of the "senile plaques" that are a hallmark of AD. Dr. Craft pointed out that evidence now indicates that the formation of these insoluble peptide plaques may actually be a defense mechanism to deal with a greater threat—smaller complexes of Aβ molecules called oligomers. Aβ oligomers are soluble, synaptotoxic (damaging to inter-neuron signaling), cause neuronal loss, and ultimately lead to cognitive impairment. In the brain, insulin helps to regulate Aβ levels (and hence levels of the oligomers). Experiments revealed a reciprocal relationship

between insulin and Aβ oligomers: treating laboratory-grown neurons with insulin could protect them from Aβ oligomer induced-synapotoxicity, but treating neurons with oligomers alone caused insulin receptors to move away from synaptic surfaces (dendritic membranes)—likely reducing insulin signaling and contributing to insulin resistance in the brain. Moreover, experiments in non-human primates showed that administering Aβ oligomers directly into the brain induced a chemical change in a protein called IRS-1 that, in other tissues, is characteristic of insulin resistance—further suggesting that Aβ oligomers play a role in insulin resistance in the brain.

Dr. Craft and her colleagues have also examined the effect of insulin resistance in the rest of the body on Aβ levels in the brain. Experiments in animal models of AD showed that inducing insulin resistance and hyperinsulinemia increased the burden of Aβ in the brain. In humans, Dr. Craft and her colleagues found through an experimental diet intervention study that 4 weeks of a diet high in saturated fat and with a high glycemic index not only had a negative impact on metabolism—increasing insulin resistance and LDL cholesterol—but also significantly increased markers of AD pathology (including Aβ) and oxidative injury detectable in the cerebrospinal fluid, a proxy for the brain. In comparison, a diet with the same caloric value but low in saturated fat and with a low glycemic index had beneficial effects on these markers. Interestingly, these results may help explain the epidemiological observations that greater saturated fat intake in mid-life increases age-related cognitive impairment and AD risk, while lower-fat diets richer in beneficial fats and complex carbohydrates decrease risk. In another set of clinical experiments, the research team found that artificially inducing hyperinsulinemia in the absence of insulin resistance induced increases in Aβ and markers of inflammation in cerebrospinal fluid, indicating that not all of the observed indications of AD-related pathology are the direct result of insulin resistance or elevated blood glucose: hyperinsulinemia may itself play a disease promoting-role. Some data suggest that older age may make people more vulnerable to these effects.

Diabetes and insulin resistance may also increase or augment AD risk through effects on vascular function. Deposition of Aβ in cerebral vasculature has been observed in mouse models. In mice genetically engineered to be vulnerable to AD and diabetes, the deposition is greater than in AD alone, and increases with age. When Dr. Craft and colleagues compared the amount of plaques and protein "tangles" (another AD marker) present in specimens from the brains of deceased persons who had had both dementia and diabetes, to that present in brain specimens of deceased persons who had only dementia, only diabetes, or neither, the results were surprising—plaques and tangles were highest in persons with dementia alone, not in persons with both dementia and diabetes. However, those with both diseases had a significantly greater prevalence of microvascular lesions in their brain specimens. The significance of this finding is not yet known—the lesions are too small to be causing problems on their own, but could be markers of some greater vascular pathology important to AD.

As Dr. Craft noted, their finding that amyloid pathology was not greatest in brains of people who died with both dementia and diabetes was quite intriguing. One possible explanation was that diabetes treatment affects amyloid plaque levels. However, Dr. Craft and her colleagues found that specimens from persons with dementia plus untreated diabetes displayed a similar plaque burden to that seen in dementia alone, while diabetes treatment with insulin (with or without additional oral medication) yielded a lower number of plaques, at a level closer to that seen in

persons with diabetes alone (treated or untreated) or neither disease—suggesting that diabetes treatment (primarily insulin) might have a mediating effect on plaques. Similar results were seen for tangles. In contrast, however, the treated-diabetes group had the highest counts of microvascular lesions. Together, these data suggest the provocative notion that dementia in individuals with untreated diabetes is likely to show the classic pathological hallmarks of AD, while microvascular lesions are more commonly characteristic of dementia in those with treated diabetes. The data also suggest that researchers investigating the links between diabetes and dementia should consider the potential effects of diabetes treatment.

Dr. Craft noted findings from her lab and others of a reduction in insulin transport across the "blood-brain barrier" in people with AD, leading to reduced insulin signaling in the brain. These observations that increasing brain insulin levels might potentially be therapeutically beneficial in AD, and/or help prevent progression of dementia. Intranasal administration of insulin is one potentially effective route. In a mouse model of diabetes, intranasal insulin administration significantly reduced the exacerbated brain atrophy that occurs in these mice as they age. Dr. Craft and colleagues are seeking to extend these findings through clinical research—the Study of Nasal Insulin to Fight Forgetfulness (SNIFF) to test whether intranasal administration can normalize brain insulin levels and improve memory and cognition in people with AD. In one recent study, adults with mild cognitive impairment or mild AD received either daily intranasal insulin at one of two different dosing levels or a placebo over the course of 4 months. The research team found that the lower dose of insulin was best for memory, but participants receiving either dosing level of nasal insulin fared better than those receiving placebo on other measures of cognition. Live imaging studies showed improvements in glucose metabolism, including in areas known to be important to AD pathology, in participants who received intranasal insulin. On the basis of these encouraging results, a larger, longer, multi-site trial is slated to begin in the fall of 2012.

In another approach, Dr. Craft and colleagues are testing the therapeutic potential of improving insulin sensitivity in AD, rather than providing additional insulin. Studies of lifestyle approaches (exercise) have shown promise for improving cognitive function and/or AD biomarkers, setting the stage for another study beginning in fall 2012. Other laboratories are testing the pharmacologic approach, using insulin-sensitizing drugs that may improve insulin signaling in the brain.

Agency Activities Pertaining to Both AD and DM – DMICC Members

NIDDK: Several NIDDK trials offer promising opportunities for ancillary studies to identify interventions that could have an impact on AD. These include the Diabetes Prevention Program and Look AHEAD, as well as a planned comparative effectiveness study focused on finding optimal medication regimens for treating diabetes over the long term. Clinical studies with a genotyping component might also be a source of samples to investigate genetic factors or biomarkers important to the association between diabetes and AD.

CDC: While there are no programs focused specifically on the relationship between diabetes, dementia, and AD, some tracking is done through epidemiological surveillance work (assessing disability, etc.) among people, including older people, with diabetes. In addition, the National Health and Nutrition Examination Survey (NHANES) included a cognitive functioning component in its 2011-2012 survey.

NIHGRI: NHGRI is supporting major genomic studies important to AD; these may also provide opportunities to gain insight into the connection between diabetes and AD.

NINDS: As part of the 2012 National Plan to Address Alzheimer's Disease, NINDS is the NIH lead on a meeting on AD-related dementias planned for 2013, which it is developing in collaboration with NIA and other ICs. The agenda includes four key topic areas: frontotemporal dementia (FTD) and AD-related tauopathies; vascular contributions; mixed etiology dementias; and Lewy body dementias. It is anticipated that the association between diabetes and AD will be discussed under vascular contributions.

Closing Comments—Dr. Judith Fradkin, NIDDK; Chair, DMICC

Dr. Fradkin noted that Dr. Tibor Roberts, NIDDK Office of Scientific Program and Policy Analysis, is taking over as DMICC Executive Secretary from Dr. Sanford Garfield, who served as the DMICC Executive Secretary for 25 years, but has recently retired from federal service. She congratulated Dr. Garfield, and expressed her appreciation for his service.

For general information about the history, goals, membership, and activities of the DMICC, please see the DMICC web page or the publication, "DMICC: Coordinating the Federal Investment in Diabetes Programs To Improve the Health of Americans."