Paris: Diabetes, Insulin, and Alzheimer Disease

Adapted from an original article by Jennifer Altman in Alzheimer Actualités, a newsletter published in French by the Ipsen Foundation. The Alzforum acknowledges the Foundation's generosity in making this summary freely available in English, as well.

17 June 2009. To survive and function, all cells need energy, which—in most animal cells—is produced from glucose and oxygen. The supply of these is tightly regulated in mammals by the hormone insulin, so it should be no surprise that diabetes, a disease in which this regulation breaks down, is being identified as a precursor to several other life-threatening conditions, including neurodegenerative diseases such as Alzheimer disease (AD) and other dementias. Evidence supporting this association and the mechanisms linking insulin to neurodegeneration were examined at the Fondation IPSEN 24th annual colloquium on Alzheimer's Disease, held in Paris on 6 April 2009. As scientists have come to expect of brain diseases, the relationship being revealed is complex. With the incidence of diabetes rising around the world, this link poses a serious challenge to public health provision. The meeting was organized by **Suzanne Craft** of the University of Washington School of Medicine, Seattle, and **Yves Christen**, Fondation IPSEN, Paris.

The brain lies behind the mouth for a good reason: animals have to eat to survive, and the brain developed in a large part to facilitate the finding and consumption of food, said **Gregory Cole**, of the University of California, Los Angeles. In mammals, food intake, body weight, and glucose production are also regulated by the brain, chiefly in the hypothalamus, the area that orchestrates the body's hormonal responses, as summarized by **Ronald Kahn**, Harvard University, Joslin Diabetes Center, Boston.

Insulin is the key hormone both in controlling the supply of glucose to cells for use in producing the energy needed for all cellular processes and in the central role in regulating feeding. The pancreas releases insulin in response to the concentration of glucose in the blood, and by attaching to receptors on cell membranes, insulin facilitates the transport of glucose into cells. Surplus glucose is stored in the liver and muscles as glycogen, which is converted back to glucose when energy demands are high. The control of glucose levels in the blood is crucial, as prolonged exposure to high concentrations of glucose damages blood vessels and the kidneys, while very low levels result in loss of consciousness and can be fatal.

Diabetes results when insulin fails to supply glucose to the cells, so that blood glucose levels rise and cells are starved of energy. Because there are two separate reasons why this happens, diabetes is classified as type 1 or type 2. In the former, the pancreas ceases to produce insulin, which has to be replaced by daily injections or pumps. In type 2, insulin is still there but the insulin receptors stop responding to it, a condition termed insulin resistance, and blood insulin levels tend to be high. Type 2 diabetes (T2D), which may have a hereditary component, generally starts in adulthood and seems to result at least in part from too much carbohydrate and fat in the diet, leading to an overload of glucose. It can be treated by changes in diet or with medication.

So what has this to do with dementia? Readers will not be surprised to learn that insulin has other functions in the brain besides regulating glucose uptake. It is involved in neuronal function, synaptic plasticity, and memory, and it contributes to the health of blood vessels in the brain. Within neurons, the signaling pathways

triggered by insulin intersect with those involved in the production of the hallmark proteins of Alzheimer disease, i.e., amyloid-β and tau. When the supply of insulin fails or its receptors become resistant, that is bound to have consequences for brain functions.

Linking Obesity and Diabetes to AD

A connection between diet and AD has long been suspected because obesity is among the established risk factors for AD, according to **Jose Luchsinger**, Columbia University Medical Center, New York. Several population studies have demonstrated cognitive decline in people with type 2 diabetes. They perform worse on tests of speed, psychomotor efficiency, executive function, learning, and memory than do people of the same age with normal glucose regulation, reported **Lenore Launer**, NIH, Bethesda, Maryland, and **Geert Jan Biessels**, University Medical Center Utrecht, The Netherlands. The deficits get larger the longer a person has had diabetes. Diabetes is also more prevalent in those diagnosed with mild cognitive decline, a condition that often precedes frank Alzheimer disease, said **Simon Lovestone** of King's College, London, UK.

The correlation between diabetes and dementia is also well established: in the U.S., 23 percent of patients over the age of 65 with dementia are reported also to have diabetes (see Alzheimer's Association). Kahn, Luchsinger, and Lovestone all estimated that diabetes increases the risk of developing any dementia by at least 100 percent and of AD by about 65 percent, with the risk increasing the longer the patient has had diabetes. A complicating factor here, Launer and Luchsinger have found, is that patients with the ε4 version of the APOE gene, a known risk factor for AD, have a much higher risk than those with the other alleles of the APOE gene. These correlations support the idea of a continuum from being overweight, to becoming obese and developing insulin resistance with high levels of insulin and glucose in the blood, to developing T2D and/or neurodegeneration and dementia, according to Luchsinger and Biessels.

Even so, as Biessels discussed, there are complications to this general assessment. First, determination of risk differs with the stage of the disease. Early on, when cognitive functions show a decrement without substantially impairing the patient's life, studies tend to be based on individual cases matched with normal controls, and the important question is the rate of deterioration. Some of these cases may never progress to dementia, while others may be excluded because they do not meet the study's criteria. At later stages, when progression is almost inevitable, population studies are more appropriate and loss of subjects through death becomes an issue.

Age is another confounding variable: for people in their forties and fifties, high cholesterol and obesity seem to be associated with a higher risk of developing dementia later in life, and hypertension is the key vascular risk factor. Whether and for how long the diabetes has been treated is yet another variable. In older people, however, as both Biessels and Luchsinger pointed out, high cholesterol, obesity, and hypertension are no longer significant as risk factors, whereas diabetes is. Luchsinger went on to suggest that once over 70, increased body weight may become protective rather than a risk, but again this is complicated as muscle is lost with aging, particularly as some people with T2D lose weight.

A further issue for population studies is the diagnosis of AD, which still can be formally confirmed only at autopsy. Frequently, that is many years after symptoms appear, when the pathology may no longer reflect that of the early disease. Even more problematic is that the plaque-and-tangle burden at autopsy often does not correlate with the patient's cognitive state, argued **Daniel Alkon**, Blanchette Rockefeller Neurosciences Institute, Morgantown, West Virginia. The problem is compounded by the association between diabetes and microvascular damage in the brain, Launer, Biessels, and Craft all thought. As well as more vascular damage, patients with treated diabetes who also have dementia have fewer plaques and tangles than those with dementia alone, said Craft (see ARF related news story).

Insulin, Food Intake, and Glucose

One of insulin's main functions in the brain is the regulation of feeding behavior by the hypothalamus. Insulin receptors are widespread in the brain, especially in the hypothalamus, entorhinal cortex and hippocampus, and the frontal lobes. In normal animals, insulin, together with another hormone, leptin, an appetite suppressant produced by fat tissue, and the neurotransmitter serotonin, which is released in the hypothalamus in response to increased insulin, all act together on hypothalamic neurons that reduce food intake, according to Kahn and to **Kyriaki Gerozissis**, INSERM, Université de Paris 7, Paris. Insulin also suppresses food intake by acting on a second group of neurons by reducing their release of peptide hormone molecules that promote feeding; by acting on these neurons, insulin also controls glucose production from the liver. Disturbances in these pathways caused by obesity may result in brain insulin and leptin signaling pathways that no longer respond to signals, that is, become resistant, which may be the link between obesity and T2D. A further twist, said Gerozissis, is that insulin and serotonin together are implicated in depression, which often accompanies diabetes and dementia.

Kahn reported on mice bred without insulin receptors in the brain, and **Lawrence Reagan**, University of South Carolina School of Medicine, Columbia, on rats whose insulin receptors in the hypothalamus are inactivated. In both models, food intake increases and they gain weight and body fat. The level of leptin in circulation goes up as a result of the extra fat, but resistance to leptin then ensues and the control of body weight breaks down. The mice lacking insulin receptors in the hypothalamus, found Kahn, also have impaired regulation of glucose output from the liver, although insulin receptors in the body are functioning normally.

Another potential consequence of defective insulin signaling is the failure of neurons to take up glucose for their energy requirements, said Reagan. Neurons are hungry cells—the brain consumes a quarter of the body's glucose supply—but they have no store of glucose. In the diabetic brain, neurons become starved, which may lead to increased damage from oxidative stress, further suppressing the glucose uptake mechanism.

The Trouble With Synapses

Plaques and tangles are the postmortem hallmarks of the AD brain, but in life, as Alkon emphasized, it is the loss of synapses that causes the real problems with memory loss. Insulin may be a key here through its other role in the brain: its involvement in neuron function, promoting the release of neurotransmitters at synaptic terminals and maintaining synaptic plasticity, actions that are necessary for efficient memory formation.

Striking parallels between animal models of diabetes and AD indicate that lack of insulin may play a part in synapse loss in AD. **Alexis Stranahan**, Johns Hopkins University, Baltimore, Maryland, and Reagan demonstrated that diabetic mice and rats genetically modified to produce amyloid plaques have deficits in spatial learning and cognitive tests, and long-term potentiation is impaired in both. In the hippocampus, a brain area involved in memory formation, Stranahan, Reagan, and Cole all showed that the neurons in diabetic rats have fewer branches with fewer spines, the points of synaptic contact with input neurons, on the remaining branches, and Cole reported similar losses in patients with AD, where they correlate with declining performance on standard memory assessments.

According to a current hypothesis, learning takes place as a result of changes at synapses instigated by convergent inputs from other neurons that stimulate various types of receptor on the neuron's surface. The action of the main neurotransmitter glutamate on its receptors is amplified by intracellular signaling pathways stimulated by insulin binding to the insulin receptor. An important enzyme activated by these signals is protein kinase C (PKC), which among other actions, promotes the release of calcium from intracellular stores. According to Alkon, PKC seems to be central to the activation of synapses in the rat hippocampus during learning tasks, as well as stimulating the expression of genes for receptors involved in learning, including the insulin receptor. As the production of insulin receptors declines with age, or as receptors become resistant to insulin, PKC is no longer activated so strongly, weakening the increase in synaptic efficacy and the growth of new synapses thought to be essential for learning.

Other insulin-stimulated paths also support spine formation and maintenance. One such pathway discussed by both Alkon and Lovestone is particularly relevant to AD because it promotes the normal cleavage of the amyloid precursor protein (APP) to produce sAPPα, which is involved in synapse formation. Insulin stimulation also helps maintain healthy neuron infrastructure by preventing the activation of GSK3. This enzyme causes the hyperphosphorylation of the tau protein, an abnormal modification leading to the formation of neurofibrillary tangles. Yet another insulin-sensitive pathway, involving the enzymes Akt and PAK, seems to be blocked by calcium influx caused by the oligomeric forms of APP, also known as ADDLs, which are thought to be deleterious to synaptic function. Cole reported that this blockage may occur only when insulin stimulation is reduced, and Alkon showed that spine formation is further supported by growth factors, such as BDNF, which in turn stimulates PKC. According to Stranahan, BDNF is reduced in both diabetic and AD brains, and Cole thinks that insulin resistance may cause resistance to growth factors.

Why Don't Mice Get AD?

A long-standing and serious problem in research into AD is that the main experimental animal models, the so-called AD transgenic mice strains that are genetically altered to express various human genes implicated in familial AD, do not adequately reproduce the pathology of the human disease. Until recently, it has been particularly difficult to recreate the tau aggregation—mice do not get neurofibrillary tangles.

In fact humans are the only species to get full-blown AD, in keeping with our unusual propensity for living well beyond our reproductive span. Lovestone argued that maybe mild insulin resistance promotes longer life, with the downside that as insulin

resistance increases with age we become more vulnerable to neurodegeneration. His laboratory is using AD-transgenic mice that also have a genetic modification to make them insulin-resistant to test the hypothesis; both he and Cole suggested that this may occur through the destabilization of many of the intracellular pathways required for maintaining healthy synapses.

Insulin resistance occurs when proteins associated with the insulin receptor—IRS-1 and IRS-2—are inactivated. Insulin resistance disrupts APP processing and promotes amyloid deposition, reported Craft. A further twist, according to Cole, is that the presence of plaques and tangles may promote resistance by uncoupling the IRS proteins from the insulin receptor, exacerbating the problems of neurons that are already compromised. Moreover, as Craft showed, high levels of insulin and triglycerides in the blood (a result of a high-fat diet and a contributory factor to the development of diabetes) are associated with an inflammatory response in the brain, which also stimulates amyloid deposition.

Many Roads Lead to Dementia

As will have already become clear, the high levels of blood glucose and compromised insulin signaling that are associated with diabetes have many consequences in the brain: the diminished supply of glucose to cells, loss of control of body weight, loss of insulin as a factor in maintaining healthy neurons and synapses, and promotion of pathological pathways in the brain.

Three other mechanisms were discussed at this workshop—vascular damage, stress, and the insulin-related growth factor (IGF-1). A high concentration of glucose in the blood in poorly controlled diabetes damages blood vessels, including those in the brain. Not only does this compromise the supply of oxygen and nutrients to the brain, but Launer suggested that it may also lead to microvascular disease, and possibly the deposition of amyloid in the vessels. Controlling blood glucose levels can reduce microvascular disease in diabetes, but it is not yet known if it reduces macrovascular disease, such as stroke, in the brain.

The brain's response to systemic stress is also affected by diabetes. In diabetic rats, Stranahan and Reagan both found that the level of the stress hormone corticosterone in circulation remains high after the stressful stimulus is removed, instead of rapidly returning to normal. Corticosterone is a glucocorticoid hormone that also regulates metabolism, produced by the adrenal glands under the control of the hypothalamus. When the level of circulating corticosterone is reduced in diabetic rats, both spatial learning and long-term potentiation improve. Glucocorticoid hormones increased the deposition of amyloid-β and tau proteins in mouse models of AD; diabetic rats also have increased deposits of tau in the brain.

One of the many functions of IGF-1 is neuroprotection, said **Ignacio Torres-Aleman**, Cajal Institute, Madrid, Spain. Insulin and IGF-1 bind to each other's receptors as well as to their own, so the two molecules reinforce each other's actions. IGF-1 is produced in the liver, and when it crosses the blood-brain barrier, the level of IGF-1 in certain brain areas increases. It contributes to cognition, probably by improving the action of the neurotransmitter glutamate at synapses, and improves memory in AD-transgenic mice.

IGF-1 also seems to promote the clearance of potentially harmful amyloid-β from the brain to the blood. Production of IGF-1 and the sensitivity of its receptors alter in

response to many of the risk factors for diabetes and AD, and high levels of triglycerides in the blood disturb the transport of IGF-1 across the blood-brain barrier. Such changes can result in an imbalance in insulin regulation in the brain, with the deleterious consequences for synaptic function discussed above, as well as impaired clearance of amyloid-β.

Prevention and Treatment

The implications of the connection between diabetes and dementia for public health are enormous. The incidence of dementia is likely to increase as the incidence of diabetes rises: Luchsinger estimated that one-third of the people with AD in northern Manhattan have diabetes. So Craft stressed that it is imperative to improve the prevention, early diagnosis, and treatment of T2D. As many speakers emphasized, the multifaceted actions of insulin and the complexity of the signaling pathways mean that there is no quick fix, and all pharmaceutical interventions must be thought through with great care.

Some simple interventions are, however, proving successful. If poor diet and lack of exercise are part of the problem, then, as Stranahan, Cole, and Craft pointed out, good diet and aerobic exercise are part of the solution. Besides generally improving people's diet, Cole reported that supplementing with the omega-3 fatty acid DHA, which is depleted in many diets, seems promising. DHA's actions include suppressing inflammation, protecting synapses, and promoting signaling pathways that inhibit GSK3 and tau phosphorylation.

Drugs such as glitazones that reduce insulin resistance have improved memory in early AD patients. Among possible interventions in signaling pathways, a compound that stimulates PKC activation is showing promise for enhancing memory, improving sAPP production, and reducing plaque formation, Alkon said. But perhaps the most surprising development is Craft's report on the intranasal administration of insulin using a simple spray. The insulin travels rapidly into the brain, and preliminary trials have produced memory improvement in people with early dementia. In a larger trial now in progress, intranasal insulin has decreased the level of the damaging form of amyloid-β in blood plasma, Craft added. Not least of its advantages is the simplicity of administration.

As Kahn recalled, long before insulin was discovered, the famous French physiologist Claude Bernard demonstrated the role of the brain in feeding behavior. It was Bernard who also defined the concept of homeostasis, the ability of the body to maintain a stable internal milieu. The link between diabetes and dementia illustrates the complexity, subtlety, and interdependence of the homeostatic control mechanisms, particularly in the brain. Finding ways to counteract pathological processes that unbalance these controls is a huge challenge, but a good start has been made.—Jennifer Altman.

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