

Evidence of Impaired Glucose Tolerance and Insulin Resistance in Patients With Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) and diabetes rarely occur together, a finding that provides a possible clue as to the development of AD. Abnormal glucose metabolism is not limited to diabetes, but also can include impaired glucose tolerance, insulin resistance, and hyperinsulinemia. AD patients have significantly varying insulin levels after drinking sugared sodas and thus may be classified as insulin resistant. After reviewing the literature on impaired glucose tolerance and insulin production in AD, we present several hypotheses as possible explanations for the relationship between insulin resistance and AD. Finally, we suggest future studies, including studies on use of thiazolidinediones (currently used in the treatment of diabetes) in AD.

Keywords

Alzheimer's disease; insulin resistance; diabetes; blood sugar; cognition

Alzheimer's disease (AD) is an incurable, deadly disease of the brain that affects more than 4 million people in the United States. Primarily a disease of old age, it affects 1 in 10 people over 65 and more than half of the population over 85. Generally speaking, AD causes degeneration of neurons, buildup of a sort of brain scar tissue (neuritic plaques and neurofibrillary tan-

gles), and overall shrinkage of the brain. Psychologically, AD results in progressive dementia, memory loss, disorientation, and confusion. The cause of AD is still unknown, although many hypotheses have been proposed. For example, some researchers have found evidence suggesting a relationship with mechanisms involved in programmed cell death, a process in which neurons "commit suicide" after a set period of time. Others have found a genetic link: In certain combinations, a gene called ApoE is associated with higher risk of AD. Given the variety of factors linked to the onset and progression of AD, it is likely that there is more than one cause. In this article, we explore the link between AD and glucose metabolism, focusing specifically on the role of insulin.

Insulin, a hormone produced by the pancreas, plays a critical role in maintaining a steady level of blood sugar. Insulin does this either by converting glucose into immediate energy for muscles or by converting it into fat, stored for later use. However, insulin in the brain plays a different role, because brain cells are able to use glucose without the help of insulin. In adults, insulin promotes brain cell growth and preservation (Devaskar, 1991). The highest concentrations of brain cells that are receptive to insulin, curiously, are in many of the same brain structures that degenerate during AD (the choroid plexus, the olfactory bulb, cerebral cortex, and the structures of the limbic system and hippocampus). This suggests

that abnormalities in blood sugar or insulin levels could have consequences for the long-term health of the brain.

ABNORMAL BLOOD SUGAR METABOLISM

Diabetes Mellitus

There are several types of abnormal blood sugar metabolism; diabetes mellitus (DM) is best known. DM is characterized by low or no insulin secretion, abnormally high blood sugar, and altered fat, carbohydrate, and protein metabolism. Of the estimated 14 million Americans with diabetes (American Diabetes Association, 2000), nearly half are over the age of 65, the same group who are at high risk for AD.

There are two forms of DM. Roughly 10% of DM is Type I, or insulin-dependent DM; Type II, or non-insulin-dependent diabetes, makes up the remaining 90% of cases (Fajans, 1996). Although both types of DM are believed to involve genetic predispositions, Type I is an autoimmune disorder in which the immune system attacks the pancreatic β -cells that produce insulin, leading to a loss of insulin production. Type II, which usually affects people later in life, is related to lifestyle or environmental triggers: obesity, high carbohydrate (sugar) consumption, extreme stress such as trauma or infection, or some combination of these factors. Type I is commonly treated with insulin injections, and Type II is treated with a combination of diet, exercise, and oral medications that lower blood sugar.

Several investigators have indicated that Type II DM and AD rarely occur together (e.g., Nielson et al., 1996), suggesting a possible relationship between glucose metabolism and AD. If DM and AD are in fact negatively related, then this

relationship could provide clues as to the cause of AD. At least three explanations for this relationship are possible. First, some aspect of AD may help to maintain normal glucose metabolism, protecting AD patients from diabetes. Second, the changes in insulin levels or glucose metabolism associated with DM may protect diabetics from developing AD. Third, there may be an additional factor that influences the development of glucose metabolism abnormalities so that the end state is DM in some cases and AD in others. If any of these three possibilities is correct, a better understanding of the link between DM and AD may result in new ways to understand one or both diseases.

Impaired Glucose Tolerance

A second type of abnormal glucose metabolism is impaired glucose tolerance (IGT). The standard test for both DM and IGT is the oral glucose tolerance test (OGTT). In this test, the patient drinks a soda with 75 g of sugar. Then, blood sugar levels are tested at regular intervals. IGT is diagnosed when blood glucose levels are higher than normal both fasting and during OGTT, but not elevated enough to be categorized as diabetic (see Table 1). Unlike diabetics, IGT patients typically have normal blood sugar levels during normal activity. Only during unusual situations are their blood sugar values abnormally high (e.g., following large con-

sumption of candy) or low (e.g., following intense physical activity).

The classifications of DM and IGT are meant to be exclusive: An individual may be classified as either diabetic or glucose intolerant, but not both. However, the distinction between Type II DM and IGT, although well defined, is not functionally distinct, and therefore an individual may move between one classification and the other several times over a lifetime. Although AD and diabetes rarely co-occur, it is possible that AD patients are instead glucose intolerant.

IMPAIRED GLUCOSE TOLERANCE AND HYPERINSULINEMIA IN AD

Studies of the blood sugar levels of AD patients report contradictory results (see Craft et al., 1993, for a summary). How should one interpret this? One possibility is that the regulation of blood sugar by AD patients changes across the course of the disease and that this factor has not been considered or controlled adequately. Seen this way, these results suggest that glucose metabolism in people with AD may be poorly regulated.

This possibility is important because fluctuating glucose levels have been proposed as a cause of death of neurons and the creation of neuritic plaques, both of which are prominent features in AD brains. These fluctuations in glucose levels

may also be associated with abnormally high levels of insulin (a condition called hyperinsulinemia), which may itself have toxic effects on neuronal tissue. However, diabetics also experience extreme fluctuations in blood sugar and yet apparently do not develop AD. From this, one can infer that if the onset of AD is related to glucose metabolism, then this relationship may be more closely associated with the negative effects of hyperinsulinemia than with those of fluctuating glucose levels. This suggests that a third type of abnormal glucose metabolism, insulin resistance with hyperinsulinemia, may influence AD.

Insulin resistance occurs when the body tissues prevent insulin from completely metabolizing blood sugar into energy. In this situation, because the insulin produced is not used efficiently, the pancreas will produce greater and greater amounts of insulin in order to achieve normal glucose levels (Flier, 1993). During hyperinsulinemia, although blood glucose levels may be normal, insulin levels are simultaneously excessively high. Studies consistently report elevated levels of insulin in the blood and cerebrospinal fluid (fluid that cushions and carries nutrients to the brain) of AD patients (Craft et al., 1998). This suggests that many AD patients may be insulin resistant and hyperinsulinemic. (Their hyperinsulinemia may be generally undiagnosed because tests on insulin levels are expensive and thus not routinely performed.) This indication of hyperinsulinemia and the blood sugar data suggest that many AD patients may be insulin resistant.

Two studies by Craft document more strongly the relation between insulin levels and the level of dementia in AD. One (Craft et al., 1998) showed that blood insulin levels increased as dementia became more severe. The other (Craft et al., 1993) found that AD patients' memory scores on a recall test were high-

Table 1. *Criteria for diagnosing diabetes and impaired glucose tolerance following the oral glucose tolerance test*

Interval	Normal	Impaired glucose tolerance	Diabetes
Fasting	<115	<140	>140
1-1 1/2 hr after ingestion	<200	>200	>200
2 hr after ingestion	<140	140-199	>200

Note. The numbers shown are blood sugar levels (mg/dl).

est during hyperinsulinemia and lowest under normal insulin conditions. These results make sense given the fact that insulin levels increase with blood sugar levels, especially among individuals who are insulin resistant. Thus, it might be the elevated blood sugar levels rather than insulin levels that lead to improved memory performance, while the associated elevated insulin levels perpetuate the neural degeneration of AD. Craft et al. (1993) asserted that those individuals with mild AD who respond to high blood sugar with strong increases in insulin levels are more likely to progress over time to a more advanced stage of AD.

INSULIN LEVELS IN AD PATIENTS AFTER OGTT

We decided to test the hypothesis that chronically high insulin levels increase the probability of neural degeneration, and therefore decrease cognitive capabilities in patients with AD. To do this, we examined the effects of fluctuating blood glucose and insulin levels in 19 mildly and moderately demented probable or possible AD patients, and 19 normal age-matched control subjects. Participants were required to be 65 or older, nondiabetic, and free of any other illness that may contribute to dementia symptoms. Blood sugar and insulin levels were tested following ingestion of sugar and diet sodas.²

There were no significant differences in blood insulin levels for AD patients and control subjects, both fasting and 60 min after glucose ingestion. What was significant, however, was the difference in variation between the groups. Insulin levels varied more for the AD patients than for control subjects, during both OGTT and fasting conditions, which leads us to conclude that these differences are not just due to individual

variance, but due to the nature of AD itself. Varying insulin levels in all situations would indicate an abnormality in the way patients with AD release and use insulin, as compared with normal adults. We can only speculate as to the long-term negative effects of widely varying insulin levels, and episodes of hyperinsulinemia, on neural degeneration.

Another significant outcome of this study was that the normal control subjects experienced improved scores on a test of short-term memory when their blood sugar levels were high, although AD patients did not show this advantage (contrary to what we expected given the results reported by Craft et al., 1993). This result indicates that although the normal elderly may experience cognitive benefits from high blood sugar, AD patients are unable to experience this benefit, possibly because of decreased glucose utilization by neuronal cells.

HYPOTHESES ON INSULIN RESISTANCE IN AD

There are several hypotheses regarding the possible role of insulin in AD. First, it is possible that fluctuating insulin levels adversely affect the utilization of glucose in the brain. Because our study showed that normal control subjects demonstrated enhanced memory when both their blood sugar levels and their insulin levels were high, one might conclude that in a nondemented brain, blood sugar and insulin together create an optimum environment for brain cells to function. Because AD patients in this study did not experience memory enhancement when their blood sugar levels were high, it is possible that abnormal levels of insulin in the body negatively affect the utilization of sugar in the brain. Because a small portion of glucose utilization in the brain is controlled by insulin, when

insulin levels fluctuate, the utilization of glucose may be decreased. Consequently, with the reduced use of glucose, neurons will deteriorate as in AD (Hoyer, 1994).

Second, it is possible that fluctuating insulin levels interact with other related protective mechanisms in the brain. Studies have demonstrated that the insulin-like hormone growth factor-I (IGF-1) protects neurons in AD. β -amyloid proteins are the building blocks of the plaques that form in the brains of AD patients, and IGF-1 has been able to stop and reverse the damage done by β -amyloid to hippocampal neurons in the rat (Doré, Kar, & Quiron, 1997). Therefore, the fluctuating insulin levels in AD patients may in some way prevent the protective actions of IGF-1.

Third, Hoyer (1994) hypothesized that when body tissues are insulin resistant, brain cells may also be insulin resistant. Therefore, it is possible that insulin resistance in brain tissue disrupts the preservative action of insulin on neurons, allowing the neurons to deteriorate as they do in AD. If this is the case, then a drug that improves insulin sensitivity (i.e., makes insulin as effective as possible) in the body may also improve the insulin sensitivity of brain cells, and therefore enhance the preservative action of insulin in the brain.

If AD is related to excessive insulin levels, we suggest one final hypothesis. Both β -amyloid and insulin are broken down by insulin-degrading enzyme (IDE; Kurochkin & Goto, 1994). IDE has been touted as the main β -amyloid-degrading enzyme in the human brain. Kurochkin and Goto found that excessively high levels of insulin in the rat brain completely block IDE from working properly. If IDE normally breaks down both β -amyloid and insulin, but is completely blocked in people with hyperinsulinemia, then the excessive amounts of insulin would cause not only a buildup of β -amy-

loid plaques in brain tissue, but also hyperinsulinemia, which in turn perpetuates the cycle. This perpetuation of the cycle may explain the progressive nature of AD. Thus, a drug that increases insulin sensitivity and efficacy, thereby reducing the need for high levels of insulin, may also stop both the cycle of hyperinsulinemia and plaque formation and the progression of cognitive decline in AD.

THE POTENTIAL USE OF THIAZOLIDINEDIONES IN AD

These hypotheses indicate that a drug that enhances insulin sensitivity may be beneficial to AD patients. Thiazolidinediones (e.g., rosiglitazone maleate, called Avandia) may hold particular therapeutic promise. Thiazolidinediones are the only available class of diabetic drugs that enhances tissue sensitivity to insulin without causing a subsequent increase in the secretion of insulin. They do this by altering the part of DNA in the cell nucleus that controls the cell's insulin sensitivity. When the cell replicates itself, it does so with this new insulin-sensitive gene.

The results of these drugs are revolutionary to the treatment of IGT and Type II DM. Because the body cells become responsive to insulin, the need for high amounts of insulin decreases, and the pancreas therefore is not overtaxed. Also, because insulin is more effective, blood sugar is better controlled. Thus, we are proposing that thiazolidinediones would be beneficial in the treatment and prevention of AD. In AD patients, these drugs should prevent hyperinsulinemia, thereby allowing IDE to destroy β -amyloid

plaques. A newly approved member of this class (e.g., Avandia) may help improve the cognitive abilities of AD patients, and subsequently halt the progression of this debilitating disease.

Because of the potential for this approach, open issues about the exact pattern of IGT in AD assume great importance. Longitudinal studies of IGT and insulin resistance over the course of normal aging would help clarify the role IGT plays in the onset and progression of AD. Because of the high variability of insulin levels in AD, longitudinal studies will also help identify any patterns in insulin production that characterize the progression of AD. A clinical trial investigating the use of one of the thiazolidinediones in AD will illuminate whether or not AD is related to impaired blood sugar and insulin utilization and whether the drug itself reverses the formulation of β -amyloid plaques in AD brains. Other interesting, basic research might examine the effect of insulin on programmed cell death in the brain, and the relationship between ApoE, which represents genetic risk for developing AD, and insulin resistance.

Recommended Reading

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Notes

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2. All 20 men and 18 women were administered psychological tests after they were given a diet soda sweetened with aspartame on one day, and an OGTT soda sweetened with 75 g of sugar approximately 1 week later. Blood sugar was tested at fasting and at 30 and 60 min following ingestion of the sodas; blood insulin levels were assessed at fasting and 60 min following ingestion of the drinks.

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