Future History

Insulin Resistance, Affective Disorders, and Alzheimer's Disease: Review and Hypothesis

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Affective disorders (ad) and Alzheimer's disease (AD) have been associated for almost a century, and various neurophysiologic factors have been implicated as common biologic markers. Yet, links between ad and AD still await elucidation. We propose that insulin resistance (IR) is one of the missing links between ad and AD. IR with hyperinsulinemia and subsequent impairment of glucose metabolism especially in ad patients may promote neurodegeneration and facilitate the onset of AD. According to our hypothesis, IR may persist even into ad remission in some patients. Persistent regional hypometabolism and vascular changes resulting from long-standing IR may lead to currently irreversible structural changes. Evidence in support of the hypothesis is reviewed and clinical implications suggested.

NUMEROUS lines of evidence link affective disorders (ad) with disorders of cognition (1,2). Cognitive impairment has been found in the euthymic phase (3) as well as the depressive and manic phases (4,5) of ad.

Depression has been considered a precursor, a prodrome, and a component of Alzheimer's disease (AD) (6), the most prevalent form of cognitive impairment in the Western world. Thus, it seems reasonable to look for a pathophysiological link underlying these disorders.

Insulin resistance (IR), a disturbance in glucose (energy) metabolism, has been described in both ad (7,8) and AD (9). Several studies have reported an association between insulin resistance (IR) and depressive disorders (7,8,10–13), and IR is a well-known precursor of non-insulin-dependent diabetes mellitus (NIDDM). Between 9.3 and 9.8 million people in the United States have diagnosed NIDDM, and another 5.4 million suffer from undiagnosed diabetes (14). The total estimated prevalence of adult Americans with hyperglycemia is 14.7% (15). Insulin resistance is a key component of NIDDM, and, in most cases, it precedes diabetes.

The pathological mechanisms behind IR remain to be fully elucidated. Cellular and molecular defects implicated in IR include dysfunctional insulin receptors, aberrant receptor signaling pathways, and abnormalities in glucose transport or glucose metabolism (16). Initially, individuals with IR maintain normal or near-normal blood glucose levels, despite a continuing decline in insulin sensitivity. In time, however, as IR gradually increases, the pancreas is less able to compensate by increasing insulin secretion (17), and progressive hyperglycemia develops.

Insulin is necessary for glucose utilization in the periphery and for neuronal survival in the central nervous system (CNS) (18). In the brain, insulin stimulates glucose uptake in glial cells (19,20) and increases glucose transporter (Glut 1) mRNA in both neurons and glia in primary culture (21). Fluctuating glucose levels as a result of defective insulin action may lead to apoptosis and formation of neuritic plaques and neurofibillary tangles (NFT), the true hallmark lesions of AD, via several interactive mechanisms: 1) by affecting glucose utilization in insulin-sensitive areas (22); 2) by modulating acetylcholine (ACh) levels in the hippocampus; and 3) by decreasing phosphorylation of the microtubule-associated protein tau (known to play a role in NFT formation) (15).

Since the human brain is almost totally dependent on a continuous supply of glucose, glucose deprivation (such as that caused by IR) would be expected to impair brain function. Impairment in glucose utilization may induce depression, which may modify behavior, and in turn, influence quality of glycemic control (22). Recurrent unavailability of glucose to the brain may have long-term sequelae in the form of treatment-resistant ad and cumulative cognitive impairment. Insulin infusion has been reported to facilitate memory in nondiabetic healthy adults (15) and in non-apolipoprotein E AD patients (23). Effects of insulin on memory in ad are unknown, but patients with ad, especially older patients, often manifest cognitive complaints and impairments (3). The highest concentrations of brain cells that are receptive to insulin, curiously, are in many of the structures of the limbic system affected in both ad and AD (24–26). IR with hyperinsulinemia and subsequent impairment of glucose metabolism especially in ad patients may promote neurodegeneration and facilitate the onset of AD.

In this article, we will review the literature describing the role of IR as a potential link between ad and AD.

According to our hypothesis (27) inadequate glucose utilization resulting from IR may underlie the hypometabolic changes in crucial brain regions observed among

patients with ad. In those with persistent IR, such changes may progress to the more permanent changes characteristic of dementia, especially in individuals with other risk factors for dementia. We propose the hypothesis as one of the links between ad and AD, and not the only link. Below we discuss: 1) evidence supporting the hypothesis; 2) some limitations of the evidence; and 3) clinical implications of the postulated relationship between IR, ad, and AD.

EVIDENCE SUPPORTING ROLE OF IR IN AD AND AD

Clinical Evidence

Among patients with bipolar disorder (BPD), prevalence of NIDDM has been reported to be two to three times that of the general population (28–31). In turn, ads have been reported to be more common in persons with diabetes than in nondiabetic persons (32), and an episode of depression increases the risk for NIDDM (13). Depression has been demonstrated to be a major factor in hospital admissions and death of persons with diabetes mellitus (33). Antidepressant therapy with serotonin reuptake inhibitors has been reported to modulate (decrease) IR in both ad (13,34) and NIDDM patients (12,35).

In turn, growing evidence suggests that a primary disruption in glucose regulation accompanies AD and contributes to the severe memory impairment that is a hallmark of the disorder (36). History of diabetes has been associated with an overall increased risk of AD but attenuated by age, gender, duration of exposure to diabetes, and the type of antidiabetic therapy utilized (37a). NIDDM increases the risk of AD even after exclusion of cardiovascular risk factors (37b). These findings are consistent with our postulate that persistent IR may lead not only to metabolic but also to vascular changes, further compounding the deficit in neuronal function.

Neurochemical Evidence

Neurochemical changes underlying both disorders can modulate and be modulated, in turn, by IR. A brief review of the role of IR in the pathophysiology of ad and AD reveals the following:

Both disorders are associated with reduced serotonergic (5-HT) activity and hyperactivity of the hypothalamo-pituitary-adrenal (HPA) axis (38–42).—Insulin facilitates transport of the serotonin precursor, tryptophan, through the blood–brain barrier (43,44) thereby increasing synthesis of serotonin. Decreased concentrations of 5-HT and its major metabolite 5-hydroxyindoleacetic acid (5-HIAA) have been demonstrated in the CNS of ad and AD patients by use of postmortem brain studies, particularly in the temporal cortex (45–52) and in the cerebrospinal fluid (CSF) (53). The serotonin reuptake inhibitor, fluoxetine, also increases peripheral sensitivity to insulin, clinically improving NIDDM (54–56).

The 5HT-IR connection could be mediated by the HPA axis. Activation of the HPA axis has been associated with impaired glycemic control and reported in both ad and AD (57,58). Numerous studies have documented increased HPA axis activity (e.g., hypercortisolemia) in association with IR (59), whereas IR may trigger perpetual hypercortisolemia and vice versa (60). It has been demonstrated that the hippocampus represents a key area in the regulation of the HPA axis activity and has a high insulin receptor concentration (61). IR furthers cortisol neurotoxicity in the hippocampus (62), which may be the *main mechanism* by which changes in endocrine homeostasis affect both mood and cognition. Alternatively, based on our hypothesis, hypercortisolemia in ad may set the stage for IR, thereby propagating the metabolic and, possibly, cognitive manifestations of ad (11,63). This postulate is complementary to the glucocorticoid cascade hypothesis of aging (64). According to that hypothesis, "advancing age is associated with increasing HPA axis dysregulation, and this dysregulation is the result of hippocampal atrophy, itself accelerated by HPA axis hyperactivity."

Insulin and glucose effects on memory function may also be mediated through neurotransmitter systems involved in memory.—Acetylcholine dysfunction has been implicated in ad and AD (65). SPECT (single photon emission computed tomography) and PET (positron-emission tomography) studies have identified decreased glucose metabolism in the cholinergic basal forebrain complex, including the limbic system and hippocampus, the very same areas affected in both ad (66–68) and AD (69,70). The impairment in glucose utilization as a result of IR may lead to decreased ACh synthesis and subsequent memory impairment. Cholinergic treatments increase regional brain glucose uptake in rodents (71) and humans (72), and, by increasing brain glucose, insulin may increase ACh synthesis and release, as well as increase memory performance (73).

The role of excitatory amino acids (i.e., glutamate) has been increasingly recognized in ad and AD (74). Glutamate may mediate glucose and insulin effects on memory performance through its effects on the hippocampus (75). In turn, insulin may modulate glutamate actions through post-synaptic activity of NMDA (N-methyl-D-aspartate) receptors (75). Therefore, decreased glucose availability under conditions of IR may lead to NMDA-receptor hypofunction with implications for both ad and AD (74).

Vascular-related risk factors associated with IR [such as coronary artery disease (CAD) and aging, among many others], provide additional evidence linking IR with ad and AD (76).—Affective disorders have been shown in epidemiological studies to increase the risk of developing CAD and to confer a poorer prognosis once CAD is present (77). AD is also associated with CAD and atherosclerosis. Apolipoprotein-E-4 (APOE-4), which is associated with early development of these diseases, carries a well-established risk for late-onset AD (78). In addition, APOE-4 has been associated with lowered parietal, temporal, and posterior cingulate cerebral glucose metabolism in AD (79,80). In AD, central and peripheral insulin abnormalities have been directly related to the severity of dementia as well as APOE genotype (15). Insulin may affect degradation of APOE by increasing the low-density lipoprotein receptor-related protein (LRP)-promoted intake of APOE-enriched

lipoprotein. LRP in turn degrades the isoform of the amyloid precursor protein (APP), a major known risk factor for AD, present in both plasma and the brain (49). Despite the discrete pathologies involved in each of these risk factors, they all impair cerebral perfusion (81a). In fact, modulation of lipid profiles through statin use has been reported to exert a strong protective effect against AD in a large case-controlled (MIRAGE, Multi-Institutional Research in Alzheimer's Genetic Epidemiology) study. In that study a 79% reduction in risk of AD was observed after adjustment for age, gender, education, ethnicity, APOE-4 genotype, and history of heart disease, stroke, and diabetes (81b).

In summary, as reviewed above, various neurochemical systems implicated in ad and AD may affect insulin regulation and lead to IR. In turn, IR may be associated with other factors and processes linking ad and AD. Examples include aging, impairment in phospholipid metabolism, and fatty acid-related signal transduction processes (82), among others. We propose that links are not mutually exclusive, but may represent pieces of the jigsaw puzzle of neuropsychiatric disorders.

Neuroimaging Evidence

Positron emission tomography with [^{18}F]fluorodeoxyglucose (FDG) determinations of glucose metabolism in both ad and AD show a consistent pattern of reduced cerebral glucose utilization in the limbic area [i.e., hippocampus, cingulate gyrus, and temporal regions (83–86), among others]. Some of these abnormalities persist in ad in spite of symptom remission (87–89). Neuroimaging studies consistently describe hypometabolism in ad, with regional decreases in metabolism being strongly linked to the cognitive impairment of major depressive disorder (90) among other "negative symptoms" [i.e., psychomotor retardation and anhedonia]. Regional hypometabolism has been shown to be reversible only in treatment responders with major improvement in both negative symptoms and cognitive functioning (90). In some studies, the hypometabolism was found to persist in the euthymic phase (91,92), and cognitive functioning in these patients remained impaired.

Persistent regional hypometabolism in the cingulate gyrus, recognized for its role in the integration of emotional behaviors, and one of the areas of earliest change in AD, was found to differentiate antidepressant treatment responders from nonresponders (87). According to our hypothesis, ad responders would be less likely to develop dementia than ad nonresponders, since nonresponders (and possibly some responders) may have IR. Compared with ad patients without IR, such patients are subject to cerebral metabolic changes over prolonged periods of time, which may lead to currently irreversible brain changes.

Imaging studies have also reported a variety of abnormalities of glucose utilization globally and in the hippocampus, cingulate gyrus, and selective temporal and subcortical regions in persons *at risk* for AD (79,80). Such patterns have been reported several years prior to the diagnosis of dementia (93). The observation that metabolic patterns predict cognitive decline in presymptomatic persons indicates that the pathophysiologic process begins well before even mild or questionable dementia is recognized

clinically. The report that depressive episodes preceding the onset of dementia by 10 years appear to double AD risk supports this postulate, as do numerous earlier findings (94).

Major disorders of insulin regulation have been associated with both ad (95) and AD (48), including diabetes, obesity, and endocrine and atherosclerotic disease. The vascular changes resulting from these illnesses may affect cerebral regions implicated in ad and AD, in addition to the previously mentioned metabolic changes (85). These changes have been documented with both H$_2$O PET and SPECT techniques. Significant regional hypoperfusion in ad (96) and AD patients (97,98) in the hippocampal/amygdaloid complex, temporoparietal cortex, and posterior cingulate gyrus predicted cognitive decline in persons at risk for AD, just as the metabolic changes did in the FDG-PET studies, described earlier (79,80).

SOME LIMITATIONS

Despite the substantial evidence in support of our hypothesis, as presented above, there are some apparent inconsistencies and limitations. For example, while AD patients may exhibit insulin resistance (9,15,23), diabetics are not known to have an increased frequency of AD despite fluctuations in blood glucose.

A negative association has been reported between a genetic risk factor for AD (APOE4) and IR (15). This finding awaits replication.

Elevated levels of insulin in AD patients (plasma and CSF) suggest that many AD patients may be insulin resistant. However, insulin levels increase with blood glucose levels, especially among individuals with IR. Therefore, elevated blood glucose levels rather than insulin levels have been postulated to be responsible for improvement in memory performance (99).

Further research identifying the components of insulin regulation involved in the pathogenesis of ad and AD is needed to elucidate the pathophysiologic link between IR and ad and AD.

CLINICAL IMPLICATIONS OF THE RELATIONSHIP BETWEEN IR AND ad AND AD

An association of ad with clinically significant weight gain (100,101) and an increased rate of diabetes (102) may be an inherent problem in ad patients or may be a side effect of treatment. Mood stabilizers (103) and antipsychotics, particularly "atypical" agents, have been reported to increase IR indirectly by promoting significant weight gain (104) with subsequent increased incidence of hyperglycemia, resulting in IR, glucose intolerance, and diabetes (105).

Early identification of a subgroup of patients with ad and IR could lead to preventive measures targeting AD, as well as earlier diagnosis and intervention. Patients with ad have a greater prevalence of IR and NIDDM (106), especially individuals with risk factors such as obesity, weight gain of more than 10% of body mass index with treatment, family history of diabetes, and hypertension. They could be evaluated for IR, as well as cognitive performance, at the beginning of treatment and at intervals thereafter. As mentioned earlier, improvement in IR has been shown upon successful antidepressant treatment of ad (12). Addition of

thiazolidinediones to treatment schedules of ad patients with IR might also be considered since thiazolidinediones are the only available antidiabetic drugs that enhance tissue sensitivity to insulin without causing a subsequent increase in the secretion of insulin. Currently thiazolidinediones are already being added for weight reduction to treatment of some ad patients (107). By preventing hyperinsulinemia, thiazolidinediones may also protect ad patients against the development of dementia. Long-term follow-up data will tell the story. Meanwhile, this approach might also be considered in the management of other diseases with IR.

CONCLUSION

The proposed hypothesis linking IR and ad and AD is pertinent for further study of biological components common to affective illness and AD. It also provides an important therapeutic target for effective management of ad, and hopefully, prevention of AD.

Future clinical studies monitoring IR throughout the management of ad will procure data needed to test the hypothesis.

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