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Relationships Between Diabetes and Cognitive Impairment

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INTRODUCTION

Like most organ systems throughout the body, the brain requires insulin and insulinlike growth factors (IGFs) to maintain energy metabolism, cell survival, and homeostasis. In addition, insulin and IGFs support neuronal plasticity and cholinergic functions, which are needed for learning, memory, and myelin maintenance. Impairments in insulin and IGF signaling, caused by receptor resistance or ligand deficiency, disrupt energy balance and disable networks that support a broad range of brain functions. Over the past several years, evidence that impairment in brain insulin and IGF signaling mediates cognitive impairment and neurodegeneration has grown, particularly in relation to mild cognitive impairment and Alzheimer disease (AD). Although amyloid deposits and phospho-tau-associated neuronal cytoskeletal lesions account for some AD-associated brain abnormalities, they do not explain the prominent and well-documented deficits in brain metabolism that begin very early in the course of the disease. Metabolic derangements in AD are similar to those in both type 1 type and 2 diabetes mellitus. However, the consequences of insulin/IGF receptor resistance and ligand deficiency include cognitive impairment and neurodegeneration caused by deficits in signaling through progrowth, proplasticity, and prosurvival pathways.

How brain insulin/IGF resistance and deficiency develop is not completely understood. Although a considerable number of studies have linked the recently increased rates of AD to

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other insulin resistance states, including obesity, type 2 diabetes mellitus (T2DM), nonalcoholic fatty liver disease (NAFLD), and metabolic syndrome, it is important to realize that most cases of sporadic (nonfamilial) AD arise with no evidence of peripheral insulin-resistance disease. This review focuses on how peripheral insulin-resistance diseases, including diabetes mellitus, contribute to cognitive impairment and neurodegeneration. The working hypothesis is that peripheral insulin resistance promotes or exacerbates cognitive impairment and neurodegeneration by causing brain insulin resistance. Mechanistically, insulin resistance with dysregulated lipid metabolism leads to increased inflammation, cytotoxic lipid production, oxidative and endoplasmic reticulum (ER) stress, and worsening of insulin resistance. Some investigators are researching the role of cytotoxic ceramides that can promote inflammation, oxidative stress, and insulin resistance. Ceramides generated in liver or visceral fat can leak into peripheral blood because of local cellular injury or death, cross the blood-brain barrier, and initiate or propagate a cascade of neurodegeneration mediated by brain insulin resistance, inflammation, stress, and cell death (**Fig. 1**). These concepts help delineate the strategies needed to detect, monitor, treat, and prevent AD as well as other major insulin-resistance diseases.

INSULIN SIGNALING

The Master Hormone

Insulin is a 5800 Da, 51 amino acid polypeptide, composed of A (21 residues) and B (30 residues) chains linked by disulfide bonds. Banting, Best and others are credited for discovering insulin in pancreatic secretions,^{1,2} and later it was shown that it reversed hyperglycemia.³ Nearly 30 years later, methods to stabilize insulin, prolong its actions, and delay its absorption emerged; 50 years after its discovery, 99% pure insulin, free of proinsulin and other islet polypeptides, was produced.⁴ Genetic engineering and yeast fermentation technology have enabled human insulin to be efficiently produced on a large scale.⁵ The field continues to evolve, with some of the latest advances directed toward replacing injectable insulin with an oral form⁶ and optimizing approaches for intranasal delivery of insulin to treat diabetes or cognitive impairment (see later discussion).⁷⁻⁹

Insulin-Stimulated Effects

The main targets of insulin stimulation include skeletal muscle, adipose tissue, and liver, although virtually all organs, tissues, and cell types are responsive to insulin. Insulin regulates glucose uptake and utilization by cells and free fatty acid levels in peripheral blood. Free fatty acids are substrates for generating complex lipids. In skeletal muscle, insulin stimulates glucose uptake by inducing translocation of the glucose transporter protein, GLUT4, from the Golgi to the plasma membrane.¹⁰ In liver, insulin stimulates lipogenesis and triglyceride storage and inhibits gluconeogenesis. In adipose tissue, insulin decreases lipolysis and fatty acid efflux.¹¹ These prometabolic effects of insulin on glucose and free fatty acid disposal help to maintain energy balance.

IGFs

Insulin is closely related to IGF-1, which is also referred to as *somatomedin C* or *mechanogrowth factor*.^{12,13} IGF-1 regulates growth during development and exerts anabolic effects

on mature organs and tissues. IGF-1 contains 70 amino acids (7649 Da) in a single chain with 3 intramolecular disulfide bridges.^{12,13} IGF-1 and IGF-2 are abundantly produced in liver and regulated by IGF-binding proteins.¹⁴

Insulin and IGF Signaling in the Brain

Within the last 15 to 20 years, information has steadily emerged about the expression and function of insulin and IGF polypeptides and receptors in the brain. It is now known that insulin and IGF signal to regulate a broad array of neuronal and glial activities, including growth, survival, metabolism, gene expression, protein synthesis, cytoskeletal assembly, synapse formation, neurotransmitter function, and plasticity,^{15,16} which are needed to support cognitive function. Insulin, IGF-1, and IGF-2 polypeptide and receptor genes are expressed in neurons¹⁵ and glial cells^{17,18} throughout the brain; but their highest levels are within structures targeted by neurodegeneration.^{15,19,20} Since genes that encode insulin, IGFs, and insulin-like peptides and their receptors have been identified in human, rodent, and drosophila brains,²¹ related signaling networks allow for local control of diverse functions, including energy metabolism.

Insulin and IGF Signal Transduction

Brain insulin/IGF signaling mechanisms are virtually the same as in other organs. The networks are activated by ligand binding to specific receptors and subsequent activation of receptor tyrosine kinases and downstream signaling through insulin receptor substrate (IRS) proteins. The attendant activation of phosphoinositol-3-kinase (PI3K)-Akt and extracellular mitogen-activated protein kinase and the inhibition of glycogen synthase kinase 3 β (GSK-3 β) promote growth, survival, metabolism, and plasticity and inhibit apoptosis.²⁰

INSULIN RESISTANCE AND NEURODEGENERATION

Insulin Resistance and its Consequences

Insulin resistance is classically defined as the state in which high levels of circulating insulin (hyperinsulinemia) are associated with hyperglycemia. The concept has broadened to include organ and tissue-related impairments in insulin signaling associated with reduced activation of the pathways. As a result, progressively higher levels of ligand are needed to achieve normal insulin actions.¹⁰ However, sustained high levels of insulin can cause insulin resistance,²² thereby worsening and possibly broadening tissue involvement. Furthermore, hyperinsulinemia impairs insulin secretion from β cells in pancreatic islets, yielding hybrid states of both insulin resistance and insulin deficiency.²²

Long-term consequences of insulin resistance include cellular energy failure (lack of fuel), elevated plasma lipids, and hypertension. In addition, chronic hyperinsulinemia vis-à-vis normoglycemia predicts future development of diabetes mellitus.²³ Insulin resistance is an independent predictor of serious diseases, including cerebrovascular and cardiovascular disease, hypertension, and malignancy.^{24–28} Insulin resistance is now front and center stage because of its link to obesity, T2DM, NAFLD, metabolic syndrome, polycystic ovarian disease, age-related macular degeneration, and AD epidemics (**Fig. 2**).

AD Occurrence and Clinical Diagnosis

AD is the most common cause of dementia in North America. Sporadic AD has no clear genetic transmission and accounts for more than 90% of the cases. In contrast, familial (heritable) AD accounts for 5% to 10% of all cases. Over the past few decades, sporadic AD has become epidemic, raising questions about environmental and lifestyle mediators of cognitive impairment and neurodegeneration.²⁹ Although the clinical diagnosis of AD is based on criteria set by the National Institute of Neurologic and Communicative Disorders and Stroke, the Alzheimer's Disease and Related Disorders Association, and the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition),³⁰ neuroimaging and a few biomarker panels have facilitated the detection of early brain metabolic derangements in AD.³¹

AD Neuropathology

Neuropathologic hallmarks of AD include neuronal loss, abundant accumulations of abnormal, hyperphosphorylated cytoskeletal proteins in neuronal perikarya and dystrophic fibers, and increased expression and abnormal processing of amyloid-beta precursor protein (A β PP), leading to A β PP-A β peptide deposition in neurons, plaques, and vessels. A definitive diagnosis of AD requires more-than-normal aging densities of neurofibrillary tangles, neuritic plaques, and A β PP-A β deposits in the brain but particularly in corticolimbic structures (Figs. 3–5). The pathognomonic molecular abnormalities that correspond with these dementia-associated structural lesions include accumulations of insoluble aggregates of abnormally phosphorylated and ubiquitinated tau, and neurotoxic A β PP-A β as oligomers, fibrillar aggregates, or plaques. Secreted neurotoxic A β PP-A β oligomers inhibit synaptic plasticity, learning, and memory via impairments in hippocampal long-term potentiation.³²

AD is a Metabolic Disease with Brain Insulin/IGF Resistance

For the better part of the last 3 decades, AD research was largely focused on the pathogenic roles of hyperphosphorylated tau and A β PP-A β , despite hints that insulin resistance and metabolic dysfunction were important factors.^{33,34} With the wealth of data collected over the past 8 to 10 years, it is fair to state that AD should be regarded as a metabolic disease that is mediated by brain insulin and IGF resistance.^{35,36} This concept is supported by the findings that AD shares many features in common with systemic insulin-resistance diseases. For example, reduced insulin-stimulated growth and survival signaling, increased oxidative stress, proinflammatory cytokine activation, mitochondrial dysfunction, and impaired energy metabolism all occur in peripheral insulin-resistance diseases as well as in AD (**Table 1**).^{20,37,38} In the early stages of disease, AD is marked by reductions in cerebral glucose utilization^{39–41}; as AD progresses, brain metabolic derangements,^{42,43} including impairments in insulin signaling, insulin-responsive gene expression, glucose utilization, and energy production, and stress worsen.^{35,36,44}

Brain Insulin and IGF Resistance and Deficiency in AD-Human Studies

Human postmortem studies have convincingly shown that brain insulin resistance with reduced activation of receptors and downstream neuronal survival and plasticity mechanisms

are consistent and fundamental abnormalities in AD.^{35,36,44} Importantly, IGF-1 and IGF-2 networks were also found to be impaired,^{35,36} meaning that their crosstalk functions were also deficient. Deficits in brain insulin and IGF signaling worsen as AD progresses,³⁵ along with declines in brain energy production, gene expression, and plasticity.³³ One of the most important realizations from these studies was that nearly all of the critical features of AD, including the activation of the kinases responsible for aberrant phosphorylation of tau and formation of neurofibrillary tangles, dystrophic neuritic plaques and neutrophil threads, A β PP and accumulation and toxicity, oxidative and endoplasmic reticulum stress, mitochondrial dysfunction, and cholinergic dyshomeostasis, can be explained by brain insulin/IGF resistance.

Does AD = Type 3 Diabetes?

Although the term type 3 diabetes is controversial, it serves to inform that the fundamental abnormalities in AD are quite similar to those present in type 1 and type 2 diabetes, except the primary target is the brain.^{35,36} Like type 1 diabetes (T1DM) in which insulin deficiency is the underlying problem, in AD, neuronal expression of insulin polypeptide gene and insulin levels in brain and cerebrospinal fluid (CSF) are reduced.^{34–36} As in T2DM, which has insulin resistance at its core, early AD is marked by insulin resistance and desensitization of insulin receptors in the brain; as AD progresses, these deficits worsen. In essence, AD can be regarded as a brain form of diabetes that has elements of both insulin resistance (T2DM) and insulin deficiency (T1DM). Although T1DM and T2DM can be associated with cognitive impairment and drive the onset or worsen the clinical course of AD, it is important to know that AD often occurs in people who do not have diabetes mellitus (**Table 2**). The notion that AD is a diabetes-type metabolic disease that is mediated by brain insulin and IGF resistance is further supported by human and experimental studies showing neuroprotective effects of glucagonlike peptide-1,⁴⁵ IGF-1,⁴⁶ and caloric restriction⁴⁷ with respect to brain aging and insulin resistance.

The inclusion of AD within the spectrum of insulin-resistance diseases opens doors for endocrinologists and specifically diabetologists to detect disease earlier in patients with overlapping organ-system involvement and also helps design and monitor the effects of treatment. The wealth of clinical, translational, and basic science data accrued by experts in the field could be extended to AD to accelerate the development of programs to better control and possibly cure AD. Similarly, the clustering of other insulin-resistance diseases, such as metabolic syndrome, NAFLD, and polycystic ovarian disease, under one analytical roof could lead to better management of these diseases and also increase the likelihood that their causes could be found.

Experimental Evidence that Type 3 Diabetes = Sporadic AD

Experimental intracerebroventricular injections of streptozotocin, a prodiabetes drug, produce deficits in brain energy metabolism,⁴⁸ impairments in spatial learning and memory, brain insulin resistance, brain insulin deficiency, and AD-type neurodegeneration but not diabetes mellitus.^{48,49} In contrast, intraperitoneal or intravenous administration of streptozotocin causes diabetes mellitus with mild hepatic steatosis and modest degrees of

neurodegeneration.^{50,51} Therefore, these experiments unequivocally demonstrate that brain diabetes (type 3) can occur independent of T1DM and T2DM and vice versa (**Fig. 6**).

Because streptozotocin is a nitrosamine-related toxin, which may be highly relevant to its overall effects, the specific consequences of brain insulin and IGF resistance are not tested by models generated with this and related compounds. To address this point, further studies were performed using small interfering RNA (siRNA) duplex molecules to silence insulin or IGF receptor expression in the brain.⁵² This approach avoided the genotoxic and nitrosative damage produced by streptozotocin.⁵⁰ The inhibition of brain insulin and IGF receptor expression with siRNA molecules was found to be sufficient to cause cognitive impairment and hippocampal degeneration with AD-type impairments in protein and gene expression.⁵² However, the phenotype was mild compared with the effects of streptozotocin. Therefore, oxidative and nitrosative damage may also be needed to produce a model that is entirely reflective of sporadic AD in humans.

Metabolic Deficits in AD: the Starving Brain

Insulin and IGF signaling regulate glucose utilization and ATP production in the brain. In AD, deficits in cerebral glucose utilization and metabolism occur early and before cognitive decline.⁵³ Therefore, impairments in brain insulin signaling are probably pivotal to AD pathogenesis.³⁶ Oxidative stress stemming from insulin resistance or other superimposed diseases can damage mitochondria, further impairing electron transport and ATP production. In addition, oxidative stress activates proinflammatory networks that cause organelle dysfunction; disinhibits proapoptosis mechanisms; stimulates A β PP expression⁵⁴ and cleavage to neurotoxic fibrils⁵⁵; and activates GSK-3 β , which promotes tau phosphorylation (**Table 3**).^{15,35,56}

The glucose transporter 4 (GLUT4) mediates glucose uptake in the brain,⁵⁷ which is abundantly expressed along with insulin receptors in the medial temporal lobe and other targets of AD.^{15,20} Insulin stimulates GLUT4 mRNA expression and GLUT4 protein trafficking from the Golgi to the plasma membrane where it engages in glucose uptake. In AD, because GLUT4 expression is preserved,³⁶ deficits in brain glucose utilization and energy metabolism vis-à-vis brain insulin/IGF resistance could be mediated in part by functional impairments in GLUT4 (ie, posttranslational mechanisms responsible for GLUT4 trafficking to the plasma membrane).

Chronic Ischemic Cerebral Microvascular Disease

Cerebral microvascular disease is a consistent feature of AD, and recognized mediator of cognitive impairment (**Fig. 7**). Postmortem studies demonstrated similar degrees of dementia in people with severe classical AD and those with moderate AD plus chronic ischemic encephalopathy. The ischemic injury mainly consists of multifocal small infarcts and leukoaraiosis (ie, extensive white matter fiber attrition with pallor of myelin staining) and prominent cerebral microvascular disease (see **Fig. 7**; **Fig. 8**).⁵⁸ T2DM and hypertension cause microvascular disease throughout the body, including the brain. Evidence that microvascular disease contributes to neurodegeneration was suggested by the finding that the medial temporal lobe, which houses the hippocampus, undergoes progressive atrophy with

advancing stages of T2DM.⁵⁹ Perhaps the regular finding of chronic ischemic leukoencephalopathy (white matter atrophy and fiber degeneration) with microvascular disease in AD is just another manifestation of brain diabetes. It is noteworthy that besides the impairments in brain glucose metabolism, white matter atrophy is one of the earliest abnormalities in AD.⁶⁰

Hyperinsulinemia causes progressive injury to microvessels. Chronic microvascular injury is characterized by reactive proliferation of endothelial cells, thickening of the intima, fibrosis of the media, and narrowing of the lumens. Mural scarring reduces vascular compliance and compromises blood flow and nutrient delivery, particularly in periods of high metabolic demand. Moreover, weakened and damaged blood vessels are leaky and permeable to toxins,^{61,62} which together could contribute to increased frequencies of microhemorrhage and perivascular white matter tissue loss in T2DM and AD. Therefore, hyperinsulinemia ultimately produces a state of chronic hypoperfusion with toxic/metabolic/ischemic tissue degeneration in the brain. These pathologic processes have not received adequate attention, and their mechanistic links to cognitive impairment in diabetes and AD are only in the rudimentary stages of investigation.

BRAIN METABOLIC DERANGEMENTS IN OTHER NEURODEGENERATIVE DISEASES

Advances in neuroimaging, including positron emission tomography, magnetic resonance imaging (MRI), functional MRI, and magnetic spectroscopy, together with molecular and biochemical biomarkers have helped demonstrate the common themes surrounding disease mechanisms among clinically and pathologically diverse sets of neurodegenerative diseases.^{63–65} For example, like AD, other major neurodegenerative diseases are associated with deficits in brain metabolism. Parkinson-dementia with Lewy bodies (DLB), frontotemporal lobar dementia, motor neuron disease, and multiple systems atrophy are all associated with brain accumulations of misfolded ubiquitinated proteins (often cytoskeletal) and increased levels of oxidative stress, neuroinflammation, autophagy, mitochondrial dysfunction, apoptosis, and necrosis.^{66–70} Parkinson disease (PD) has epidemiologic links to diabetes mellitus,⁴⁵ and experimental PD is associated with insulin resistance in the basal ganglia.⁷¹ Finally, impairments in insulin and IGF signaling exist in human brains with PD or DLB, although the nature and distribution of abnormalities differ from those in AD.⁷² Therefore, many sporadic human neurodegenerative diseases could potentially be approached from diagnostic and therapeutic perspectives through knowledge gained in endocrinology and specifically diabetology.

UNDERLYING CAUSES OF BRAIN INSULIN RESISTANCE IN AD

Aging

Insulin and IGF resistance increase with aging, whereas longevity is associated with the preservation of insulin/IGF responsiveness.^{73–75} Furthermore, evidence suggests that chronic stress over a lifespan damages cells because of excessive signaling through insulin/IGF-1 receptors.⁷⁶ Correspondingly, neuronal overexpression of IRS2 leads to increased fat

mass, insulin resistance, and glucose intolerance with aging.⁷⁷ These findings suggest that chronic overuse of insulin/IGF signaling networks, which occurs with hyperinsulinemia and insulin resistance, accelerates aging.

Declines in growth hormone levels and metabolism also promote aging because of the anabolic deficiencies that accelerate metabolic dysfunction.⁷⁸ Because growth hormone deficiency promotes obesity⁷⁹ and obesity promotes insulin resistance and hyperinsulinemia, aging-associated declines in growth hormone could be a cause of insulin resistance.⁸⁰ Because this concept is broadly applicable to insulin resistance–related degenerative diseases, efforts should be made to improve our understanding of cellular aging, with the goal of preventing or delaying the onset of neurodegeneration.

Arguments could be made that insulin resistance, cognitive impairment, and AD are inevitable consequences of aging⁸¹ because aging-associated chronic low-grade inflammation^{82,83} causes insulin resistance.^{83,84} Because inflammation and insulin resistance increase oxidative stress, over time, reactive oxygen species and advanced glycation end-products accumulate, driving mitochondrial dysfunction, DNA damage, and cell death cascades,⁸⁰ which are pivotal to aging-associated cognitive impairment and brain atrophy.

On the other hand, opposing arguments offer an alternative perspective and suggest that other intrinsic host factors, lifetime exposures, and lifestyle choices dictate the quality of aging and propensity to develop insulin-resistance diseases. An excellent example of this phenomenon exists with respect to postpolio syndrome, in which people who recovered from childhood poliomyelitis exhibit high rates of motor neuron disease as middle-aged adults.^{85,86} During childhood, recovery from poliomyelitis was enabled by the vigorous regenerative and reparative activities of the youthful plastic central nervous system (CNS). However, with aging, the regenerative capacity of the CNS declines. Individuals develop postpolio motor neuron disease because the underlying previously damaged motor neuron system gets exposed, resulting in significant weakness caused by denervation myopathy.^{87,88} In contrast, aging of the previously undamaged CNS results in mild weakness and reduced mobility; this suggests that chronic enrichment and protection of neuronal circuitry may be required to maintain excellent brain function throughout the normal human lifespan.

Lifestyle Choices and Aging

Obesity, T2DM, NAFLD/nonalcoholic steatohepatitis (NASH), metabolic syndrome, and AD have grown in prevalence to epidemic proportions in many societies.^{29,89,90} In recent years, countries throughout the world have witnessed rapid increases in the prevalence rates of insulin-resistance diseases and their consequences in nonaged individuals, including adolescents and children.⁸¹ These trends have been linked to obesity and sedentary lifestyles. Because the spectra of insulin resistance–related diseases are nearly identical across different age groups, it could be argued that certain lifestyles, habits, and behaviors cause disease by accelerating aging. By the same token, lifestyle modifications could potentially retard aging and defer or prevent aging-associated insulin-resistance diseases, including neurodegeneration.

Obesity and Cognitive Impairment

Obesity significantly increases the risk for cognitive impairment and leads to brain insulin resistance because of the disruption of homeostatic mechanisms.^{11,91–93} Concerns about obesity's effects on the brain arose from studies showing an increased risk for mild cognitive impairment (MCI) or AD-type dementia in individuals with glucose intolerance, deficits in insulin secretion, T2DM, obesity/dyslipidemic disorders, or NASH.^{20,94–96} Other studies correlated obesity with deficits in executive function^{96,97} and eventual development of AD.⁹⁸ These concepts were confirmed in experimental animal models of diet-induced obesity with T2DM.^{47,91,99,100} Perhaps the most convincing evidence that obesity contributes to cognitive impairment was provided by studies showing that weight-loss reversal of insulin resistance improves cognitive performance^{101,102} and neuropsychiatric function¹⁰³ and that adherence to Mediterranean diets reduces metabolic risk for AD.¹⁰⁴

T2DM

The molecular and biochemical abnormalities in AD mimic the effects of T2DM on skeletal muscle and NASH on liver. Epidemiologic and longitudinal studies demonstrated increased risks for MCI or AD in people with glucose intolerance, T2DM, obesity/dyslipidemic disorders, or deficits in insulin secretion.^{105–107} More recently, investigators linked increased rates of cognitive impairment to chronic hyperglycemia,¹⁰⁸ which precedes the diagnosis of T2DM. Similarly, postmortem studies revealed that peripheral insulin resistance contributes to cognitive impairment and AD progression,^{109,110} whereas experimental studies showed that diet-induced obesity with T2DM leads to deficits in spatial learning and memory,⁹⁹ brain atrophy with brain insulin resistance, neuroinflammation, oxidative stress, and deficits in cholinergic function.^{91,111}

NAFLD/NASH

Several studies have shown that cognitive impairment and neuropsychiatric dysfunction occur with steatohepatitis caused by obesity, alcohol abuse, chronic hepatitis C virus infection, Reyes syndrome, or nitrosamine exposure.^{111–114} Mechanistically, steatohepatitis (ie, inflammation with fatty liver disease) increases ER stress, oxidative damage, mitochondrial dysfunction, and lipid peroxidation, which together drive hepatic insulin resistance.⁹³ Hepatic insulin resistance dysregulates lipid metabolism and promotes lipolysis,¹¹⁵ which increases the production of toxic lipids, including ceramides, which further impair insulin signaling, mitochondrial function, and cell viability.^{93,116,117} Liver disease worsens as ER stress and mitochondrial dysfunction exacerbate insulin resistance,¹¹ lipolysis, and ceramide accumulation.^{118–120}

Experimental models of NAFLD with T2DM and visceral obesity are associated with brain atrophy, neurodegeneration, and cognitive impairment.^{56,91,100,111,114} In humans with NASH, the rates of neuropsychiatric disease, including depression and anxiety,¹²¹ and the risks for developing cognitive impairment¹²² are increased. In fact, cognitive impairment and neuropsychiatric dysfunction correlate more with steatohepatitis and insulin resistance than obesity or T2DM.^{123,124} Therefore, the potential roles of steatohepatitis and hepatic insulin resistance in relation to neurodegeneration must be considered. To this end, the author and colleagues hypothesized that increased levels of cytotoxic ceramides generated in

liver (or visceral adipose tissue) could cause neurodegeneration.^{56,100,111,114} In humans and experimental models with steatohepatitis, ceramide gene expression and ceramide levels are increased regardless of the cause.^{19,20,91,125–128} Correspondingly, CNS exposures to cytotoxic ceramides cause AD-type molecular and biochemical abnormalities in vitro^{129,130} and cognitive-motor deficits, brain insulin resistance, oxidative stress, metabolic dysfunction, and neurodegeneration with features similar to AD in vivo.¹²⁸ Ex vivo treatment of frontal lobe slice cultures with long-chain ceramide-containing plasma from obese rats with steatohepatitis produces neurotoxic responses with impairments in viability and mitochondrial function.¹²⁵ This concept illustrates how peripheral insulin-resistance diseases might cause or contribute to cognitive impairment and neurodegeneration.

Metabolic Syndrome

Metabolic syndrome is a cluster of disease processes that pivots around insulin resistance, visceral obesity, hypertension, and dyslipidemia.¹³¹ Metabolic syndrome increases the risk for coronary artery disease, atherosclerosis, and T2DM and is frequently associated with NAFLD/NASH, proinflammatory and prothrombotic states, and sleep apnea.¹³¹ Studies have linked peripheral insulin resistance,¹³² visceral obesity,¹³³ and metabolic syndrome^{134–136} to brain atrophy, cognitive impairment, and declines in executive function. These associations sound an alarm in light of the recent increases in the prevalence of metabolic syndrome among adults and children.¹³⁷ If T2DM, obesity, metabolic syndrome, and NAFLD/NASH could actually be demonstrated to serve as cofactors in the pathogenesis and progression of neurodegeneration, then aggressive efforts would be needed to treat and prevent the full spectrum of systemic insulin-resistance diseases. Accordingly, antihyperglycemic or insulin sensitizer agents have already been shown to reduce AD clinical manifestations and pathology.^{56,138–143}

SUMMARY

Brain insulin/IGF resistance initiates a cascade of progressive oxidative stress, neuroinflammation, impaired cell survival, mitochondrial dysfunction, dysregulated lipid metabolism, and ER stress. Continued compromise of neuronal and glial functions causes cognitive impairment and the eventual development of neurodegeneration. Because many of the molecular and cellular abnormalities in AD exist in systemic/peripheral insulin resistance, such as in obesity, T2DM, and NAFLD/NASH, common mechanisms of insulin and IGF resistance should be investigated. By regarding these clinically diverse diseases as fundamentally related on molecular, biochemical, and perhaps etiologic bases, their clustering beneath an umbrella term of *insulin resistance spectrum disorders* could accelerate the discovery of new treatments and improve the understanding of disease pathogenesis and progression.

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KEY POINTS

- Alzheimer disease is a neurodegenerative disease associated with impairments in glucose metabolism and insulin resistance in the brain.
- Many of the molecular and biochemical defects in Alzheimer disease are identical to those in either type 1 or type 2 diabetes mellitus as well as other insulin-resistance disease states.
- Peripheral insulin-resistance disease states, including diabetes, obesity, and nonalcoholic fatty liver disease, are associated with cognitive impairment and can exacerbate Alzheimer disease, (ie, cause it to progress).
- Therapeutic measures used for diabetes show efficacy in the early and moderate stages of Alzheimer disease.
- Endocrinologists and diabetologists should play a larger role in the early detection and monitoring of cognitive impairment in obese and/or diabetic patients.

Fig. 1.

Concept: Systemic insulin-resistance diseases mediate brain insulin/IGF resistance and neurodegeneration. In T2DM, nonalcoholic steatohepatitis (NASH), visceral obesity, and metabolic syndrome, dysregulated lipid metabolism causes oxidative stress and increased levels of toxic lipids, such as ceramides, which can cross the blood-brain barrier to promote brain insulin resistance. The molecular and biochemical consequences of brain insulin resistance are nearly identical to those in non-central nervous system organs and tissues (ie, oxidative stress, inflammation, ER stress, metabolic impairments, and local accumulations of neurotoxic lipids, [eg, ceramides]). However, the structural consequences are that the brain undergoes atrophy with progressive cell loss, white matter fiber and myelin degeneration, and synaptic disconnection, leading to impairments in learning and memory. Ultimately, a self-reinforcing cycle of neurodegeneration gets established, making it impossible to halt neurodegeneration by one mechanism. Instead, multipronged efforts must be used, including treatment of systemic insulin-resistance diseases. AβPP, amyloid-beta precursor protein; HDL, high-density lipoprotein; PCO, polycystic ovarian syndrome.

Fig. 2. Spectrum of insulin-resistance diseases affecting different primary target organs. Overlap among these diseases occurs frequently, and rates have increased with the obesity epidemic.

Fig. 3.

Human brain with severe AD showing extreme atrophy of the cortex with thinning of gyri (*tan curvy hill-like structures*) and widening of sulci (*grooves between gyri*). (A) Lateral surface of right hemisphere-frontal lobe to right, parietal is toward the middle, occipital to left, and temporal at the base. (B) Same half-brain as in (A) showing medial surface with frontal pole to the left, occipital on the right. Frontal, parietal, and temporal lobes are markedly atrophic. (C, E, G) Represent histologic images of the left temporal lobe and (D, F, H) represent the right temporal lobe shown at low (C, D), medium (E, F) and high (G, H) magnifications to illustrate more severe atrophy of the cortex (Ctx) with extensive replacement of neurons in the right compared with left temporal lobe. Note absence (loss) of large neuronal cell bodies in (H) compared with (G). Both sides are severely damaged; but asymmetry is not uncommon, meaning that neurodegeneration does not arise in all brain regions or progress in both hemispheres at the same time ([C–H] Luxol fast blue, hematoxylin-eosin, original magnifications: C, D = $\times 20$; E, F = $\times 100$; G, H = $\times 400$).

Fig. 4.

Left: Coronal section through the right cerebral hemisphere showing extreme atrophy of the hippocampus, thalamus, and white matter, with compensatory enlargement of the ventricles. Right: Histologic section through the hippocampus stained to illustrate abundant senile plaques and neurofibrillary tangles replacing the normal architecture (Bielschowsky silver impregnation) (original magnification $\times 100$).

Fig. 5.

Typical histopathologic lesions in AD. Arrows point to the following: (A) dense core plaques in cerebral cortex (Congo red); (B) amyloid precursor protein-amyloid beta (A β PP-A β) immunoreactivity in cortical plaques; (C) phospho-tau immunoreactive neurofibrillary tangles accumulated in cortical neurons; and (D) ubiquitin immunostained neurofibrillary tangles in neurons. Fine dotlike and linear structures in the background neuropil of (C, D) represent dystrophic neuritis. Immunoreactivity was detected with biotinylated secondary antibody, horseradish peroxidase conjugated streptavidin, and diaminobenzidine (brown precipitate). Background structures were stained with hematoxylin (original magnifications: A, C, D = $\times 200$; B = $\times 100$).

Fig. 6.

Experimental models of peripheral and brain insulin resistance that lead to neurodegeneration. siRNA, small interfering RNA.

Fig. 7.

Microvascular disease contributes to cognitive impairment and neurodegeneration in AD. (A) Arteriolosclerosis and capillary sclerosis are associated with fibrotic thickening of vessel walls and extreme narrowing of the lumens (*arrow*). (B) Arteriosclerosis results in chronic ischemic injury with rarefaction of white matter fibers (loss of dense Luxol fast blue myelin staining in vicinity of blood vessels [*arrow*]). Note fibrosis of vessel walls and perivascular microhemorrhages in center. These abnormalities reflect increased stiffness and reduce vascular compliance, together with weakness and leakiness of vascular walls. (C) Marked fibrotic thickening and damage to vessel wall caused by destruction (clearing) of the media. Tissue surrounding vessel in center is lost. Adjacent myelin is stained blue (Luxol fast blue). (D) Large area of perivascular tissue loss and further pallor adjacent to lacunar infarct. Note small vessels with tiny lumens and rigid fibrotic vessels in the middle of the perivascular lacunar infarct ([A–D] Luxol fast blue, hematoxylin-eosin).

Fig. 8.

White matter fiber loss in AD. Myelin is produced by oligodendrocytes, which are insulin and IGF-1 responsive. Insulin resistance impairs oligodendrocyte function. In AD, brain insulin/IGF-1 resistance develop early in the course of neurodegeneration, and the earliest abnormalities include impairments in glucose metabolism and white matter atrophy. White matter from the (A) anterior frontal, (B) posterior frontal, (C) parietal, and (D) occipital lobes (Luxol fast blue). The normal appearance of staining is depicted in (D), an area least affected by AD. The pink coloration in (A, B) reflect loss of myelin and myelinated fibers. The extreme pallor of myelin staining in (C) corresponds to the severity of neurodegeneration and extensive fiber loss.

Table 1

Mechanisms and consequences of cellular injury and degeneration in insulin-resistance diseases

Mediator of Injury	Mechanisms and Consequences of Injury
Inflammation	Activation of proinflammatory cytokines
Stress	ER, oxidative, and nitrosative stress; DNA, RNA, protein damage and adduct formation
Cell injury/death	Activation of proapoptosis pathways
Metabolic deficiencies	Dysregulated lipid metabolism, lipid peroxidation
Mitochondrial dysfunction	Reduced ATP production, increased reactive oxygen species
Vascular	Stress and mechanical injury, ischemic tissue damage, end-organ hypertensive injury with microhemorrhages and toxin exposure

Table 2

Comparison of T1DM, T2DM, and type 3 diabetes

Target Effects	T1DM	T2DM	Type 3 Diabetes
Insulin ligand	Reduced	Increased	Reduced
Insulin receptor	Unaffected or increased	Reduced activation	Reduced activation and expression
Glucose utilization	Decreased	Decreased	Decreased
Primary targets	Pancreas, (brain)	Skeletal muscle, adipose tissue, vessels	Brain: neurons, white matter
Secondary targets	Brain, retina, blood vessels, kidneys, skin, peripheral and autonomic nerves	Brain, blood vessels, kidneys, peripheral and autonomic nerves, retina, skin	Brain satiety centers with increased proneness to obesity

Table 3

Role of insulin resistance or insulin deficiency in the molecular and pathologic features of AD

Alzheimer Pathology	Role of Insulin Resistance/Deficiency
Phospho-tau neuronal cytoskeletal lesions	Increased activation of GSK-3 β caused by inhibition of insulin signaling and increased oxidative stress
Amyloid pathology	Formation of toxic amyloid-beta soluble oligomeric fibrils
Cell injury/death	Activation of proapoptosis pathways; inhibition of prosurvival mechanisms; increased endoplasmic reticulum, oxidative, and nitrosative stress; macromolecular adducts
Impaired glucose utilization	Reduced glucose uptake, impaired GLUT4 function, reduced signaling downstream of the insulin receptor through IRS, PI3K, and Akt
Impaired learning and memory	Inhibition of growth pathways needed for synapse formation and remodeling, reduced cholinergic and other neurotransmitter functions, impaired neurogenesis
Microvascular disease	Hyperinsulinemia in T2DM, possibly local insulin resistance
White matter atrophy	Cerebral microvascular disease, inhibition of myelin maintenance by oligodendrocytes
Cholinergic functional deficits	Inhibition of choline acetyltransferase expression, which is regulated by insulin/IGF-1
Mitochondrial dysfunction	Oxidative stress-induced DNA damage leading to reduced ATP production and increased levels of reactive oxygen species
Neuroinflammation	Activation of proinflammatory cytokines