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Therapeutic targets of brain insulin resistance in sporadic Alzheimer's disease

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Abstract

Growing evidence supports roles for brain insulin and insulin-like growth factor (IGF) resistance and metabolic dysfunction in the pathogenesis of Alzheimer's disease (AD). Whether the underlying problem stems from a primary disorder of central nervous system (CNS) neurons and glia, or secondary effects of systemic diseases such as obesity, Type 2 diabetes, or metabolic syndrome, the end-results include impaired glucose utilization, mitochondrial dysfunction, increased oxidative stress, neuroinflammation, and the propagation of cascades that result in the accumulation of neurotoxic misfolded, aggregated, and ubiquitinated fibrillar proteins. This article reviews the roles of impaired insulin and IGF signaling to AD-associated neuronal loss, synaptic disconnection, tau hyperphosphorylation, amyloid-beta accumulation, and impaired energy metabolism, and discusses therapeutic strategies and lifestyle approaches that could be used to prevent, delay the onset, or reduce the severity of AD. Finally, it is critical to recognize that AD is heterogeneous and has a clinical course that fully develops over a period of several decades. Therefore, early and multi-modal preventive and treatment approaches should be regarded as essential.

Keywords

Amyloid; Anti-oxidants; Brain diabetes; Brain insulin resistance; Incretins; Insulin; Insulin sensitizers; Liver-Brain-Axis; Metal Chelation; Neuroprotection; Nitrosamine; Oxidative Stress; Polyphenols; Statins; Streptozotocin; Tau; Type 3 diabetes

2. INTRODUCTION

The gold standard for definitively diagnosing AD is to perform a postmortem examination of the brain, with the objective of demonstrating beyond-normal aging associated densities of neurofibrillary tangles, neuritic plaques, and amyloid-beta 40–42 kD fragments of amyloid beta precursor protein (AβPP-Aβ) deposits in corticolimbic structures, bearing in mind that neurodegeneration frequently involves multiple other cortical regions as well. The common thread among these characteristic lesions is that they harbor insoluble aggregates of abnormally phosphorylated and ubiquitinated tau, and neurotoxic AβPP-Aβ in the form of

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oligomers, fibrillar aggregates, or extracellular plaques. Secreted AβPP-Aβ oligomers have been demonstrated to be neurotoxic and to inhibit hippocampal long-term potentiation, i.e. synaptic plasticity (1).

To improve diagnosis and treatment, we must learn to connect the development and progression of neurodegeneration with molecular, biochemical, physiological, neuro-imaging, and clinical abnormalities in AD. Several strategies could be taken to advance this process. One is to consider the roles of other major abnormalities, including loss of neurons, fibers, and synapses, disruption of the cortical-laminar architecture, gliosis, proliferation of dystrophic neurites, and neuro-inflammatory responses. A second matter is to recognize and possibly embrace the significance of the considerable overlap among various subtypes of neurodegeneration with respect to their underlying cellular, molecular, biochemical, and structural abnormalities. The former approach could provide more options for discovering neurodegeneration and the latter could help define panels of biomarkers for diagnosing AD and distinguishing it from other forms of dementia. A third point is that the recognition of shared abnormalities among different neurodegenerative diseases may help to identify treatments and preventive measures that could be effective in all or most of them. Through the use of neuro-imaging, including positron emission tomography (PET) scanning, magnetic resonance imaging (MRI), functional MRI, and magnetic spectroscopy, combined with increasingly sophisticated molecular and biochemical analyses of postmortem brain tissue, it has become evident that neurodegenerative diseases share in common abnormalities in brain metabolism, accumulations of mis-folded ubiquitinated proteins (often cytoskeletal), oxidative stress, neuroinflammation, autophagy, and cell loss mediated by mitochondrial dysfunction, apoptosis, or necrosis. Therefore, attention must be paid to these multi-process mechanisms of neurodegeneration in considering therapeutic targets. Although this review focuses on AD, the concepts are very likely applicable to other major neurodegenerative diseases including fronto-temporal dementias, multiple systems atrophy, Parkinsonism-Lewy Body Dementia, and motor neuron diseases.

3. ALZHEIMER'S DISEASE: A BRAIN FORM OF DIABETES MELLITUS

Growing evidence supports the concept that Alzheimer's disease (AD) is fundamentally a metabolic syndrome in which brain glucose utilization and energy metabolism are impaired (2–6). These abnormalities have been linked to brain insulin and insulin-like growth factor (IGF) resistance with disablement of pathways needed for survival, gene expression, and plasticity in neurons (2). Inhibition of insulin/IGF signaling results in increased: 1) activity of kinases that cause tau to become hyper-phosphorylated; 2) accumulation of AβPP-Aβ; 3) production of oxidative and endoplasmic reticulum (ER) stress; 4) oxidative damage to proteins, RNA, DNA, and lipids; 5) mitochondrial dysfunction; 6) neuro-inflammation; and 7) activation of pro-death cascades. The attendant down-regulation of target genes needed for cholinergic homeostasis, compromises learning, memory, and cognition.

Clues that AD actually represents a metabolic disease emerged from studies showing that deficits cerebral glucose utilization mark the early stages of disease (7–12), and that progression of metabolic abnormalities correlates with worsening of AD symptoms (13, 14). Recent studies showed that AD is associated with insulin and insulin-like growth factor

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(IGF) resistance and insulin/IGF deficiency in the brain, and are accompanied by significant and progressive abnormalities in the expression of genes and activation of kinases that are regulated by insulin and IGF (2–6). In fact, most if not all of the major abnormalities in AD, including deficits in choline acetyltransferase, hyper-phosphorylation of tau, increased oxidative stress, neuro-inflammation, activation of pro-AβPP-Aβ cascades, and metabolic failure could be attributed to impaired insulin/IGF actions in the brain (5). Correspondingly, experimental down-regulation or depletion of brain insulin receptors is sufficient to cause cognitive impairment and neurodegeneration with features that overlap with AD (15–19). In AD brains, deficits in insulin/IGF signaling are due to the combined effects of insulin/IGF resistance and deficiency. Insulin/IGF resistance is manifested by reduced levels of insulin/IGF receptor binding and decreased responsiveness to insulin/IGF stimulation, while trophic factor deficiency is associated with reduced levels of insulin polypeptide and gene expression in brain and cerebrospinal fluid (CSF) (4–6, 20–22). In essence, AD can be regarded as a form of brain diabetes that has elements of both insulin resistance and insulin deficiency. To consolidate this concept, we proposed that AD be referred to as, “Type 3 diabetes” (5, 6).

4. SYSTEMIC DISEASE FACTORS CONTRIBUTING TO BRAIN INSULIN/IGF RESISTANCE AND AD NEURODEGENERATION

Aging is the most dominant risk factor for AD. This means that a host of intrinsic, environmental, and epigenetic factors that contribute to the process of aging establish the circumstances needed for neurodegenerative diseases to become manifested. The corollary is that the factors governing development of neurodegenerative diseases are not strictly genetic and therefore can be modified or prevented. Correspondingly, epidemiologic, clinical, and experimental data indicate that peripheral insulin resistance associated with obesity, Type 2 diabetes mellitus (T2DM), metabolic syndrome (dyslipidemic states), and non-alcoholic steatohepatitis (NASH), can all mediate brain insulin/IGF resistance, and thereby contribute to the pathogenesis of mild cognitive impairment (MCI), dementia, or AD (3, 4, 22–29). More recently, human and experimental animal studies have provided new information about the causes and effects of brain insulin resistance and deficiency, particularly in relation to cognitive impairment (5, 6, 19, 30–33). The near globalization of the obesity epidemic is sounding alarms that now draw all of our attentions (23, 34). However, expansion of the literature often yields confusion from conflicting results and variability in study design. In order to develop logical and novel approaches for treating and preventing neurodegeneration based on the brain insulin resistance hypothesis, three main questions must be addressed: 1) Do T2DM and other peripheral insulin resistance states cause neurodegeneration, including AD? 2) Do T2DM and other peripheral insulin resistance disease states principally serve as co-factors in the pathogenesis of cognitive impairment and neurodegeneration? or 3) Do T2DM and AD fundamentally represent the same disease processes occurring in different target organs and tissues? These questions are addressed below.

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4.1. Contributions of obesity and T2DM to cognitive impairment and neurodegeneration

Epidemiologic studies demonstrated that individuals with glucose intolerance, deficits in insulin secretion, or T2DM have a significantly increased risk of developing mild cognitive impairment (MCI) or AD-type dementia. Longitudinal studies further suggested that T2DM (35, 36) and obesity/dyslipidemic disorders (37) correlated with eventual development of MCI, dementia, or AD (35, 38–43). However, one study showed that obesity itself, with or without superimposed T2DM, increased the risk for MCI, AD, or other forms of neurodegeneration (44), suggesting that systemic factors related to obesity, besides T2DM, can promote neurodegeneration. On the other hand, although a relatively high percentage of individuals with MCI or dementia have T2DM, peripheral insulin resistance, or obesity, the vast majority of patients with AD do not have these diseases. To gain a better understanding of the contributions of T2DM and obesity to neurodegeneration, attention must be given to postmortem human and experimental animal studies.

In general, the arguments made in favor of the concept that T2DM or obesity causes AD are not founded; however, the concept that peripheral insulin resistance disease states contribute to cognitive impairment and AD pathogenesis or progression does have a sound basis. Against a causal role are the findings that, postmortem human brain studies demonstrated no significant increase in AD diagnosis among diabetics (45), and similarly abundant densities of senile plaques and rates of neurofibrillary tangle pathology were observed in subjects with T2DM compared with normal aged controls, although peripheral insulin resistance was more common in AD than with normal aging (46). Since neurofibrillary tangles and dystrophic neurites are hallmarks of AD and correlate with severity of dementia, the abovementioned findings in human postmortem studies indicate that T2DM alone is not sufficient to cause AD. On the other hand, in experimental mouse and rat models, chronic high fat diet (HFD) feeding and diet induced obesity (DIO) with associated T2DM, do cause cognitive impairment with deficits in spatial learning and memory (47, 48). Moreover, experimental obesity with T2DM causes mild brain atrophy with brain insulin resistance, neuro-inflammation, oxidative stress, and deficits in cholinergic function (49, 50).

An important qualifier concerning these studies is that the associated brain abnormalities in diabetes and obesity syndromes were typically modest in severity, and devoid of many important structural lesions that characterize AD, i.e. neurofibrillary tangles. Therefore, observations in both in humans and experimental models suggest that while obesity or T2DM can be associated with cognitive impairment, mild brain atrophy, and a number of AD-type biochemical and molecular abnormalities in brain, including insulin resistance and oxidative stress, they do not cause significant AD pathology. Instead, the findings suggest that T2DM, obesity, and probably other peripheral/systemic insulin resistance states serve as co-factors contributing to the pathogenesis or progression of neurodegeneration. The significance of these results is that therapeutic strategies designed to treat T2DM, obesity, and systemic insulin resistance could help slow the progress or reduce the severity of AD, but they will not likely prevent it altogether. Correspondingly, a number of studies have already demonstrated that treatment with hypoglycemic or insulin sensitizer agents can be protective in reducing the incidence and severity of AD brain pathology (51).

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4.2. Pathological processes contributing to cognitive impairment and neurodegeneration in states of systemic insulin resistance

T2DM, obesity, and peripheral insulin resistance may contribute to MCI, dementia, and neurodegeneration as a result of chronic hyperglycemia, peripheral insulin resistance, oxidative stress, advanced glycation end-products accumulation, insulin degrading enzyme activation, inflammation, and/or microvascular disease (42). Chronic hyperglycemia, peripheral insulin resistance, oxidative stress, and advanced glycation end-product accumulation can cause progressive injury to vessel walls and eventual fibrosis. Insulin degrading enzyme has a role in the processing AβPP, and in states of insulin deficiency or resistance, insulin degrading enzyme may be rendered more available for AβPP cleavage and attendant AβPP-Aβ deposition in vessel walls. Finally, the contribution of dyslipedemic states associated with T2DM, obesity, and hepatic steatosis is such that toxic lipids, particularly ceramides, can cause insulin resistance. Their increased levels in peripheral blood in peripheral insulin resistance disease states may contribute to progressive insulin resistance in cerebral vessels and brain parenchyma, accounting for the excessive overlap of AD with cerebral micro-vascular disease.

4.2.1. Vascular factors—The role of cerebral microvascular disease deserves particular attention because of its long recognized association with AD. Cerebrovascular disease can additively impact the development and progression of dementia by causing multifocal ischemic lesions, focal infarcts in structures targeted by AD, or leukoaraiosis with pronounced attrition of white matter fibers (52). Diabetes mellitus causes arteriosclerosis, in part due to chronic hyperinsulinemia, which injures blood vessels, causing intimal thickening, scarring, and leakiness (53–58). In addition, hyperinsulinemic diabetics who also carried at least one ApoE-ε4 allele were found to have a compounded risk for developing AD, whereas non-diabetic, ApoE4-ε4 negative individuals showed significantly lower densities of AβPP-Aβ plaques and neurofibrillary tangles by postmortem examination.

4.2.2. Neurotoxic lipids—Recent studies suggest that cognitive impairment correlates more with hepatic steatosis and insulin resistance than obesity or T2DM (59–65). Correspondingly, neurocognitive deficits and brain insulin resistance occurred primarily when chronic high calorie feeding resulted in visceral obesity with steatohepatitis. Moreover, a number of examples showed that high fat intake and obesity were not required, and instead, toxin exposures that caused steatohepatitis with hepatic insulin resistance also resulted in neurodegeneration and cognitive impairment (19, 33, 49, 50, 66, 67). These observations suggest that hepatic insulin resistance may mediate neurodegeneration.

Hepatic insulin resistance dysregulates lipid metabolism, resulting in increased oxidative and ER stress, mitochondrial dysfunction, and lipid peroxidation (68, 69). Sustained hepatic insulin resistance leads to increased lipolysis (70) and the generation of toxic lipid e.g. ceramides, which further impair insulin signaling, mitochondrial function, and cell viability (69, 71, 72). Ceramides are lipid signaling molecules (73) that cause insulin resistance (74–76) by activating pro-inflammatory cytokines (73, 77, 78) and impairing PI3 kinase-Akt activation (79–82). Hepatic ceramide production increases in various models of steatohepatitis, including diet-induced obesity (DIO) and low-level nitrosamine exposure

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(19, 33, 49, 66, 67), and each is associated with cognitive impairment, brain insulin resistance, and neurodegeneration. This point led us to formulate the hypothesis that, in the settings of obesity, T2DM, and other peripheral insulin resistance states, cognitive impairment is mediated via a liver-brain axis of neurodegeneration (83–85).

4.2.3. Liver brain axis hypothesis—In essence, cognitive impairment with neurodegeneration and brain insulin resistance is caused by the increased generation of ceramides in liver, which enter peripheral blood, and cross the blood-brain barrier to produce neuronal insulin resistance, oxidative stress, and molecular and biochemical abnormalities that lead to AD (86). This hypothesis is supported by experiments showing that parenteral administration of cytotoxic ceramides produces sustained impairments in spatial learning and memory with neurodegeneration and brain insulin/IGF resistance, similar to the effects of DIO with T2DM and NASH Preliminary studies showed that chemical inhibitors of ceramide biosynthesis enhance insulin sensitivity, and treatment with peroxisome proliferator-activated receptor (PPAR) agonists, e.g. PPAR-α (GW7647), PPAR-δ (L-160,043), or PPAR-γ (F-LLeu), which improve insulin responsiveness and reduce oxidative stress (33, 87–89), decrease hepatic ceramide generation, serum ceramide levels, cognitive impairment, and neurodegeneration in models of DIO with T2DM and steatohepatitis (90). Therefore, we propose that peripheral insulin resistance diseases contribute to neurodegeneration, including AD, by increasing production of neurotoxic ceramides that cause brain insulin resistance.

5. CENTRAL NERVOUS SYSTEM PATHOGENIC FACTORS MEDIATING PRIMARY BRAIN INSULIN/IGF RESISTANCE (TYPE 3 DIABETES)

A compelling argument has been made that AD represents a brain form of diabetes mellitus (5, 6). AD is associated with progressive brain insulin resistance in the absence of T2DM, obesity, or peripheral insulin resistance (5, 6, 31, 32), and the molecular, biochemical, and signal transduction abnormalities in AD are virtually identical to those that occur in both T1DM and T2DM (5, 6, 35, 91–95). This hypothesis is supported by experimental studies in which, the administration of intracerebroventricular streptozotocin, a glucosamine-nitrosourea pro-diabetes compound, resulted in cognitive impairment with deficits in spatial learning and memory, brain insulin resistance and insulin deficiency, and AD-type neurodegeneration, but not diabetes mellitus (19, 96–99). In contrast, parenteral administration of streptozotocin causes diabetes mellitus with relatively mild degrees of hepatic steatosis and neurodegeneration (96, 100–102). The alkylating properties of streptozotocin cause DNA damage, and uptake of streptozotocin by insulin producing cells, i.e. pancreatic islet beta cells, leads to insulin deficiency and hyperglycemia (Type 1 diabetes). However, the broader effects of low or high dose streptozotocin treatments suggest that the glucosamine-nitrosourea actions extend well beyond inducing toxic injury to insulin producing cells. These observations suggest that diabetes mellitus syndromes with impairments in insulin signaling and energy metabolism, and increased oxidative stress, mitochondrial dysfunction, and cell death, can selectively target one or more organ-systems including liver, skeletal muscle, adipose tissue, kidney, or brain. This concept is not unique since vascular, autoimmune, and malignant neoplastic diseases can also selectively or

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differentially afflict different organ systems. But, what pathological or physiological factors are responsible for the selective occurrence of insulin/IGF resistance in the brain?

5.1. Role of tau pathology in the pathogenesis of type 3 diabetes

Neurofibrillary tangles and dystrophic neuritis represent the major neuronal cytoskeletal lesions that correlate with dementia in AD. These structural abnormalities contain aggregated and ubiquitinated insoluble fibrillar microtubule-associated proteins, particularly tau. (103, 104). Tau protein becomes gets hyper-phosphorylated due to inappropriate activation of kinases, such as GSK-3β. Consequently, tau protein misfolds and self-aggregates into insoluble fibrillar structures that form neurofibrillary tangles, dystrophic neurites, and neuropil threads (105). Accumulation of fibrillar tau disrupts neuronal cytoskeletal networks and axonal transport, leading to synaptic disconnection and neurodegeneration (105). In addition, prefibrillar tau can aggregate into soluble neurotoxic oligomers that cause synaptic disconnection and neuronal death (106). Although the key steps leading to tau hyper-phosphorylation and aggregation, could be explained on the basis of brain insulin/IGF resistance (107–110), due to the associated decreased signaling through phosphoinositol-3-kinase (PI3K), Akt (28, 29), and Wnt/β-catenin (111), and increased activation of GSK-3β (112–116), tau hyper-phosphorylation mediated by other mechanisms such as increased activation of cyclin-dependent kinase 5 (cdk-5) and c-Abl kinases (117, 118), and inhibition of protein phosphatases 1 and 2A (105, 118, 119), could lead to oxidative stress and neuro-inflammation, which are inhibitory to insulin/IGF signaling.

5.2. Contributions of Amyloid-β neurotoxicity in type 3 diabetes

In AD, amyloid precursor protein (AβPP) expression and processing are dysregulated, resulting in the accumulation of AβPP-Aβ (Aβ) soluble neurotoxic oligomeric fibrils, and insoluble aggregated fibrils (plaques). Increased AβPP expression and altered proteolysis result in formation and accumulation of 40 or 42 amino acid length Aβ peptides that can aggregate. The causes of Aβ accumulation and toxicity in sporadic AD are still unknown. However, experimental evidence supports opposing arguments that brain insulin resistance with attendant oxidative stress and neuro-inflammation promotes Aβ accumulation and toxicity, and that Aβ toxicity causes brain insulin resistance.

Insulin stimulation accelerates trafficking of Aβ from the trans-Golgi network, where it is generated, to the plasma membrane, and insulin stimulates Aβ extracellular secretion (120) and inhibits its intracellular accumulation and degradation by insulin-degrading enzyme (121, 122). Therefore, impaired insulin signaling can disrupt both the processing of AβPP and clearance of Aβ (123). On the other hand, accumulation of Aβ disrupts insulin signaling by competing with insulin, or reducing the affinity of insulin for binding to its own receptor (124, 125). In addition, AβPP oligomers inhibit neuronal transmission of insulin-stimulated signals by desensitizing and reducing the surface expression of insulin receptors, and intracellular AβPP-Aβ directly interferes with PI3 kinase activation of Akt, which leads to impaired survival signaling, increased activation of GSK-3β, and hyper-phosphorylation of tau. Since IGF-1 or IGF-2 suppression of GSK-3β activity (126) reduces the neurotoxic effects of AβPP (127–130), the neuro-protective properties of these and related trophic factors could be exploited for therapeutic purposes in AD.

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5.3. Stress factors in the pathogenesis of brain insulin resistance

Insulin and IGF signaling regulate glucose utilization, metabolism, and ATP synthesis needed for cellular homeostasis and broad ranging functions. Deficits in cerebral glucose utilization and energy metabolism occur early in AD, either prior to, or coincident with initial stages of cognitive decline (22, 131, 132). Correspondingly, impairments in brain insulin and IGF signaling mechanisms correlate with severity of AD (6). Since glucose transporter 4 (GLUT4) regulates brain glucose uptake and utilization, and GLUT4 expression and function are stimulated by insulin, brain insulin resistance could readily account for the deficits in energy metabolism that begin early in the course of AD. Deficits in energy metabolism lead to increased oxidative stress, mitochondrial dysfunction, and pro-inflammatory cytokine activation (16, 109, 133). Oxidative stress promotes the accumulation of reactive oxygen (ROS) and reactive nitrogen species (RNS) that attack subcellular organelles, resulting in adducts with DNA, RNA, lipids, and proteins, and attendant compromise of their structural and functional integrity. Consequences include, loss of cell membrane functions, disruption of the neuronal cytoskeleton with attendant synaptic disconnection, neurotransmitter deficits, and impaired neuronal plasticity, and neuro-inflammation. Neuro-inflammatory responses in microglia and astrocytes increase oxidative stress, organelle dysfunction, and pro-apoptosis signaling. However, neuro-inflammation can also contribute to brain insulin/IGF resistance because it stimulates AβPP expression (134), and aberrant AβPP cleavage, deposition, and toxic fibril formation in the brain (130, 135–139). In addition, persistent oxidative stress and neuro-inflammation lead to constitutive activation of kinases e.g. GSK-3β, which promote aberrant hyper-phosphorylation of tau. Therefore, although brain insulin/IGF resistance causes oxidative stress, neuro-inflammation, and energy dyshomeostasis, oxidative stress can also precipitate or exacerbate brain insulin/IGF resistance and thereby worsen neurodegeneration (5, 26, 33).

5.4. Reverberating loop of neurodegeneration

In sporadic AD in which brain diabetes is the main or only manifestation of insulin/IGF resistance in the body, the initiating and etiological factors are not known. However, experimental data cited above, support seemingly opposing arguments that hyper-phosphorylated tau, aberrant amyloid-beta processing, oxidative stress, and neuro-inflammation both cause and can be caused by brain insulin/IGF resistance. The significance of the aggregate results is that, once the cascade of neurodegeneration has been established, it can be exacerbated and perpetuated by the very pathological processes that are caused by the initiating factors. Therefore, the process of neurodegeneration can cyclically spiral toward more advanced stages of disease, and ultimately result in permanent changes that are no longer amenable to treatment.

6. ENVIRONMENTAL/EXPOSURE FACTORS POTENTIALLY MEDIATING BRAIN INSULIN/IGF RESISTANCE AND NEURODEGENERATION

The argument that aberrant phosphorylation of tau, AβPP protein processing, and neuroinflammation are causal, i.e. major initiating factors in the pathogenesis of brain insulin/IGF resistance is weakened by the fact that these pathological processes have no known primary causes, and a large number of studies have thoroughly documented that

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intracerebral treatment with streptozotocin, a pro-diabetes drug, not only causes brain insulin/IGF resistance, but also leads to increased tau phosphorylation, AβPP accumulation, and neuro-inflammation (15, 18, 19, 33, 140). In addition, intracerebral delivery of short interfering RNA (si-RNA) duplexes to inhibit insulin, IGF-1, or IGF-2 receptor expression and signaling in the brain or cultured neurons was found to be sufficient to increase tau phosphorylation, AβPP-Aβ expression, oxidative stress, mitochondrial dysfunction, and neuronal death (141). Together, the intracerebral streptozotocin and si-RNA studies support a primary role for brain insulin/IGF resistance (brain diabetes) as the initiating factor in the pathogenesis of AD and its protein molecular and biochemical lesions. However, the missing link is what could possibly cause brain (type 3) diabetes? The answer is most likely connected to the same factors responsible for our epidemics of Type 2 diabetes, non-alcoholic steatohepatitis, and metabolic syndrome.

6.1. Environmental toxins/exposures as mediators of type 3 diabetes

Despite overwhelmingly convincing data that AD represents a brain form of diabetes, conclusions drawn from the intracerebral streptozotocin experiments raise questions because streptozotocin is generally not available to humans. Over the past several years, our group has wrestled with this puzzle. The startling realization that streptozotocin is actually a nitrosamine-related compound that is routinely used to generate models of Type 1 and Type 2 diabetes, prompted us to probe potential links between nitrosamine exposures and diabetes mellitus or AD. Over the past several decades, Western societies have endured continuous and growing exposures to environmental and food-related nitrosamines. The curves corresponding to exposure rates through processed foods precede and parallel those for AD and diabetes mortality, irrespective of age group (34). Since nitrosamines are mutagenic and cause cancers in many organs, we posed the question as to whether low and limited exposures to nitrosamines could cause insulin resistance instead of cancer.

We conducted experiments using brief exposures to sub-mutagenic doses of nitrosamine compounds that are commonly found in processed and preserved foods, e.g. N-nitrosodiethylamine (NDEA), and determined the long-term effects on insulin/IGF signaling networks in the body, liver, and brain. Those studies revealed that low-dose NDEA exposures cause T2DM, non-alcoholic steatohepatitis, visceral obesity, cognitive impairment, and AD-type neurodegeneration with peripheral, hepatic, and brain insulin resistance (66, 67), similar to the effects of streptozotocin. Moreover, the adverse effects of NDEA on neuro-cognitive deficits, peripheral, hepatic, and brain insulin resistance, steatohepatitis, and neurodegeneration were exacerbated by chronic high fat diet feeding (142, 143). Therefore, depending on the structure of the compound, dose, and route of administration, nitrosamines and related chemicals can cause insulin resistance diseases in multiple different target organs, including brain. These results provide evidence that the relatively recent epidemics of sporadic AD, T2DM, and non-alcoholic steatohepatitis/metabolic syndrome could be mediated by environmental or dietary exposures (34), and show that insulin resistance diseases with essentially the same underlying cellular abnormalities, can develop in various organs and tissues. Moreover, these findings correspond with the overlapping increases in prevalence of various insulin resistance diseases, and the very frequent co-occurrences of AD with obesity, T2DM, of NASH (46),

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which did not exist prior to 1980, and is not accounted for by aging of the population (34). It is noteworthy that nearly two decades ago, mutagenic nitroso compounds were recognized to also cause insulin resistance diseases (144–146).

7. POTENTIAL THERAPEUTIC TARGETS FOR AD

The metabolic/brain insulin resistance hypothesis can account for nearly all abnormalities that characterize the AD neurodegeneration cascade, including progressively increased oxidative stress and ROS generation, mitochondrial dysfunction, cell death, loss of synaptic plasticity, deficits in cholinergic homeostasis, increase expression of AβPP, hyper-phosphorylation of tau, compromised myelin maintenance, and neuro-inflammation. Correspondingly, it is important to bear in mind that AD fundamentally represents a metabolic disease associated with the same molecular, biochemical, and cell signaling abnormalities identified in peripheral insulin resistance diseases. Therefore, it may be possible to treat or prevent progression of AD based on stage and severity of brain insulin resistance, similar to approaches used to treat T2DM, obesity, non-alcoholic steatohepatitis, and metabolic syndrome. At the same time, it is important to recognize that AD is the end result of a neurodegeneration cascade that targets and progressively cripples different aspects of cellular physiology and homeostasis. Therefore, it should anticipated that while mono-therapies may be appropriate, and instead, multi-pronged approaches will likely be needed to support a range of nervous system functions and minimize cellular injury and toxicity as the disease progresses.

7.1. Targeting insulin deficiency (Table 1)

AD is associated with brain insulin deficiency (reduced brain and CSF levels), with or without associated systemic insulin resistance or T2DM. Proposed therapeutic strategies designed to rectify brain insulin deficiency in AD, are supported by the findings that: 1) diabetic patients that are well-managed with insulin exhibit significant improvements in memory and slowing of AD progression; 2) elderly diabetics that were treated with insulin had lower densities of AD lesions compared with non-diabetic controls; 3) insulin administration improves cognition and memory in AD, and insulin stimulated cognition is correlated with increased levels of norepinephrine in both plasma and CSF (147); 4) hyper-insulinemic euglycemic clamping enhances cognition and attention in patients with AD; and 5) experimental intracerebral or intravenous treatments with insulin improve memory, cognition, evoked brain potentials, and neurotransmitter function (123). Although attractive and seemingly simple, a foremost consideration is that the subject population consists of elderly individuals who would be at increased risk complications resulting from inadvertent bouts of hypoglycemia, e.g. traumatic falls that could be debilitating or life-threatening, and metabolic insults to various organs, including brain. Moreover, the effectiveness of insulin therapy may be dependent upon simultaneously increased levels/availability of glucose, and may not improve memory if CSF AβPP-Aβ42 levels are markedly elevated due to insulin resistance (148). Therefore, systemic insulin therapy for patients with AD is not feasible.

7.1.1. Intranasal insulin therapy—Intranasal insulin can be administered to AD subjects because it does not produce the harmful side-effects of systemic insulin treatment.

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Intranasal insulin increases brain insulin levels and improves performance on declarative memory tasks while having little effect on plasma glucose and insulin levels (149). In addition, intranasal insulin delivered via an electronic atomizer, improves attention and increases the AβPP-Aβ 40/AβPP-Aβ42 ratio (150). Reducing the relative amounts of AβPP-Aβ42 should be neuroprotective as AβPP-Aβ42 is the neurotoxic form of the secreted peptide. In a controlled clinical trial, ApoE-∈4-negative individuals were found to benefit significantly from intranasal insulin, as manifested by improvements in cognitive performance (149). The fact that ApoE∈4+ subjects failed to benefit from the same treatment suggests that intranasal insulin, as well as other pro-metabolic therapies for AD, may have to be tailored according to particular genetic risk factors and biomarkers of disease.

7.1.2. Insulin stimulating/releasing hormones (incretins)—As an alternative to insulin, incretins, such as glucagon-like peptide-1 (GLP-1), may help restore insulin levels in the brain. GLP-1 is an insulinotropic peptide that is generated by cleavage of proglucagon protein. GLP-1 is rapidly degraded by dipeptidyl peptidase-4, and therefore is quite safe. GLP-1 stimulates insulin gene expression and secretion, and suppresses glucagon. GLP-1 lowers blood glucose in individuals with T2DM (151, 152), and it restores insulin sensitivity. The dual actions of incretins in stimulating insulin secretion and enhancing insulin responsiveness make GLP-1 and related molecules very attractive for treating AD. Like insulin, GLP-1 stimulates neuritic growth in CNS neurons and exerts neuroprotecive actions against glutamate-mediated excitotoxity, oxidative stress, trophic factor withdrawal, and cell death (153–155). In addition, inhibition of dipeptidyl peptidase-4, which degrades GLP-1, reduced oxidative and nitrosative stress, inflammation, memory impairment, and AβPP-Aβ deposits in an AD transgenic mouse model (156). Importantly, GLP-1 can cross the blood-brain barrier, and may effectively reduce brain AβPP-Aβ burden in AD (151, 152, 157). With the realization that GLP-1 has a short half-life and therefore limited practical use for long-term therapy, synthetic long-lasting analogues of GLP-1 have proven to be effective in preserving cholinergic neuron function (158). The development of GLP-1 receptor agonists, such as Geniposide or Extendin-4, which harbor the same neuro-protective and neuro-stimulatory properties as GLP-1 (159), but have longer half-lives (153, 157, 160, 161), may provide effective and standardized long-term options for treating brain insulin resistance diseases such as AD. Finally, a future approach could be to genetically modify mesenchymal or stem cells to provide sustained delivery of neuro-stimulatory and neuro-protective agonists (162–164), including GLP-1 (165).

7.2. Targeting insulin resistance

Human clinical and postmortem studies have documented that AD is associated with brain insulin resistance, with or without associated systemic insulin resistance or T2DM.

7.2.1. Anti-hyperglycemic agents—Metformin is a biguanide anti-hyperglycemic drug that is used to treat T2DM. Metformin suppresses gluconeogenesis and enhances glucose uptake and insulin sensitivity. Metformin protects against neurological complications of T2DM, including cognitive impairment and cerebral vascular disease (166). Although metformin treatment was found to increase the generation of both intra- and extracellular

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AβPP-Aβ due to increased expression of beta-secretase 1 (BACE1), administration of insulin plus metformin paradoxically provides significant neuroprotection, reduces AβPP-Aβ levels, and decreases the severity of AD pathology, including AβPP-Aβ neuritic plaques, and oligomeric AβPP-Aβ-mediated down-regulation of the insulin receptor. Therefore, while metformin mono-therapy may be harmful due to its exacerbation of AD-type neurodegeneration (167), when combined with insulin, it may benefit elderly patients in the early stages of AD, by significantly improving cognitive performance and slowing the rate of neurodegeneration.

7.2.2. Insulin sensitizers—Peroxisome proliferator-activated receptor (PPAR) agonists are steroid hormone super family ligand-inducible transcription factors that enhance insulin sensitivity, modulate glucose and lipid metabolism, stimulate mitochondrial function, and reduce inflammatory responses (168–171). Three classes of PPARs are recognized, PPAR-α, PPAR-δ, and PPAR-γ. All 3 are expressed in the adult brain, although PPAR-δ is most abundant, followed by PPAR-γ (6, 33, 88). PPAR agonist treatments improve cognitive performance in experimental animal models (33, 172) and in humans with AD or MCI (87, 89, 173). The PPAR-γ agonist, rosiglitazone, has been most widely studied in human clinical trials. In addition to its insulin sensitizing and anti-inflammatory properties, rosiglitazone, like metformin, increases expression of the GLUT4 glucose transporter and glucose metabolism. Moreover, PPAR agonists such as, rosiglitazone, can enhance the therapeutic effects of metformin+insulin.

In a small double-blind, placebo-controlled trial, rosiglitazone treatment significantly preserved performance on delayed recall and attention tasks relative to the placebo-treated group, which continued to decline (174), but a later study found that rosiglitazone therapy mainly helped preserve cognition in patients who were ApoE ∈4-negative (175). More recently, the outcome of a rosiglitazone monotherapy, randomized double-blind placebo controlled phase III study was negative with respect to improvements in objective cognitive assessments, but highly statistically significant based on clinical and caregiver impression (176). Potential explanations for these disappointing results include the following: 1) effective treatment of neurodegenerative diseases may require a different isoform of PPAR agonist, i.e. PPAR-δ, since PPAR-δ is abundantly expressed in the brain, and previous studies showed that PPAR-δ agonist treatment more effectively prevented AD-type neurodegeneration and neurocognitive deficits compared with PPAR-α and PPAR-γ agonists (33); 2) the biodistribution of the PPAR agonists may not have been optimized based on the structure of the compounds; and 3) mono-therapy may not be sufficient, and instead the combined administration of a PPAR agonist with insulin or GLP-1 and metformin may be required to effectively treat AD-associated brain insulin resistance and metabolic dysfunction.

Insulin resistance states lead to metabolic imbalances with disturbances in carbohydrate and lipid metabolism. Perturbations in lipid metabolism result in states of lipotoxicity, which further increase insulin resistance. PPARs, including PPAR-γ, regulate energy balance by promoting dissipation or deposition of energy. PPAR-γ-coactivator 1alpha (PGC1-alpha) induces gene expression that promotes differentiation, and increases fatty acid oxidation via expansion of mitochondrial capacity and function (177). PGC1alpha binds to nuclear PPAR-

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γ, which then enables its interactions with various transcription factors that regulate mitochondrial biogenesis. In essence, PGC1alpha is an important negative regulator of oxidative stress, mitochondrial dysfunction, lipotoxicity, and insulin resistance (177–179). The relevance of these data to AD is that genetic deficiencies in PGC1 alpha increase proneness to neurodegeneration (179, 180). This suggests that PGC1 alpha may represent an excellent therapeutic target for AD, and possibly other major neurodegenerative diseases as well.

7.3. Targeting tau pathology

Hyper-phosphorylation of tau promotes misfolding and aggregation of oligomeric fibrils. Subsequent protein ubiquitination results in the formation of insoluble, fibrillar aggregates and paired helical filaments, which comprise the cores of neurofibrillary tangles, neuropil threads, and dystrophic neurites, i.e. the structural hallmarks of AD neuropathology. Tau hyperphosphorylation is mediated by inappropriate and sustained activation of kinases, including glycogen synthase kinase-3β (GSK-3β) (181), cyclin-dependent kinase -5 (Cdk-5), p38 MAPK, and c-jun kinase (JNK) (182, 183), and inhibition of phosphatases that dephosphorylate tau, e.g. protein phosphatase-2A (183). Insulin resistance leads to increase activation of GSK-3β as well as other kinases due to combined effects of inhibiting PI3K-Akt and increased oxidative stress. The increased oxidative stress induced by the accumulation of misfolded, aggregated cytoskeletal proteins exacerbates insulin resistance and neuroinflammation. Therefore, treatment with chemical inhibitors of one or more AD-relevant kinases may reduce the rates of neurofibrillary pathology and help prevent progressive brain insulin resistance.

Several studies focused on the role of GSK-3β because, in addition to promoting tau hyper-phosphorylation, high levels of GSK-3β activity lead to alterations in AβPP processing and increased neuronal death (181, 184–186). Approaches to therapeutically inhibit GSK-3β activity have mainly included the use of lithium chloride, and to a lesser extent, indigoids (181, 184–187). In several uncontrolled or retrospective human studies, it was found that prior use of lithium therapy protected against dementia and was associated with better performance on cognitive tests (188–191). In addition, chronic lithium treatment reduced the prevalence rates of AD and the brain activity levels of GSK-3β, and it increased the levels of brain-derived neurotrophic factor in subjects at risk for early onset familial AD, (192). However, a subsequent randomized, single-blind, short-term (10 weeks) placebo-controlled multicenter trial proved disappointing in that performance on standardized cognitive function tests was not significantly improved, and no significant reductions in CSF GSK-3β activity were detected (193). On the other hand, those data should to be interpreted with caution because of the short duration of the trial compared with earlier retrospective studies.

7.4. Reducing amyloid burden to restore insulin responsiveness

Research in the field of AD has extensively focused on finding safe and effective means of depleting the brain of toxic AβPP-Aβ deposits, reducing the formation of toxic AβPP-Aβ-derived diffusible ligands (ADDL) and oligomers, preventing AβPP-Aβ fibrillarization and aggregation, increasing brain clearance of AβPP-Aβ peptides, and decreasing abnormal cleavage of AβPP (194). The central hypothesis is that AβPP-Aβ peptides are neurotoxic,

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promote amyloid plaque formation, and mediate tau hyper-phosphorylation, fibrillarization, and neurofibrillary tangle formation (195). Efforts to deplete the brain of toxic AβPPAβ led to the development of AβPP-Aβ-targeted immunotherapy. Although AβPP-Aβ active immunization with AβPP-Aβ peptides, or passive delivery of AβPP-Aβ-specific antibodies can effectively clear AβPP-Aβ plaques from human and experimental animal brains (196), the end results proved not very encouraging because the AβPP-Aβ instead accumulated in vessels, increasing propensity for micro-hemorrhage (197). Moreover, the human subjects continued to decline and died with end-stage AD (198, 199). The treatments are not free of side effects because subjects can develop vasogenic cerebral edema (196, 199), i.e. pro-inflammatory responses with increased microglial activation, cerebral amyloid angiopathy, and accumulation of soluble neurotoxic oligomeric AβPP-Aβ (200). Furthermore, although the administration of passive humanized AβPP-Aβ antibody can clear AβPP-Aβ from the brain (201), it has been difficult to demonstrate clinically significant improvements in progression from mild or moderate to severe dementia (202).

An approach to prevent the build-up of toxic AβPP-Aβ and formation of ADDLs is to inhibit the expression or activity of enzymes that aberrantly process and cleave AβPP. AβPP-Aβ is generated by sequential proteolysis by beta secretases, then gamma-secretases (203). Presenilins (PS), which are often mutated in early onset familial AD, form the catalytic component of gamma-secretases, which mediate intramembranous cleavage of type 1 transmembrane proteins, including AβPP (204). Mutation of PS genes leads to premature and excessive brain accumulations of AβPP-Aβ (204). To inhibit abnormal processing of AβPP and accumulation of toxic AβPP-Aβ, gamma secretases have been targeted (205, 206). Although this approach seems promising for lowering plasma, CSF, and brain AβPP-Aβ burden (203, 207), the objective clinical therapeutic responses have been minimal or undetectable (205, 208, 209). Worse yet, these drugs are highly toxic due to concurrent inhibition of Notch signaling (203, 206), which mediates neuronal plasticity, cognition, and long-term memory (210). To circumvent toxicity problems, efforts are underway to develop Notch cleavage-sparing gamma secretase inhibitors (211, 212), but clinical trial results are not yet known.

Insulin accelerates trafficking of AβPP-Aβ from the trans-Golgi network to the plasma membrane, and extracellular secretion of Aβ (120), and impaired insulin signaling disrupts the processing of AβPP and clearance of AβPP-Aβ (123). Therefore, by addressing the underlying causes of insulin/IGF resistance, we may be able to effectively and safely reduce AβPPAβ burden in the brain. This point is reinforced by the finding that IGF-1 and IGF-2 are neuroprotective as they reduce the neurotoxic effects of AβPP (127–130). On the other hand, AβPP oligomers and ADDLs inhibit neuronal insulin-stimulated signals, blocking PI3 kinase activation of Akt, which leads to impaired survival signaling, increased activation of GSK-3β, and resultant hyper-phosphorylation of tau. This suggests that efforts to reduce AβPP oligomer fibrillarization as a means of restoring brain insulin sensitivity should continue to be pursued.

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7.5. Antioxidant and anti-inflammatory drugs (Table 1)

Antioxidants help maintain mitochondrial homeostasis, neuronal activities, and cell survival. Oxidative stress plays a pivotal role in the pathogenesis and progression of AD. Sources of oxidative stress include, impaired insulin signaling, fibrillarization of oligomeric AβPP-Aβ and tau, mitochondrial dysfunction, micro-vascular disease, accumulation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), and inflammation (213). Although it has not yet been determined which source of oxidative stress in most critical to neurodegeneration and cognitive impairment, some doubt has been cast upon the role of AβPP-Aβ since in a longitudinal analysis, significant reductions in plasma AβPP-Aβ42 in subjects treated with various anti-inflammatory agents, was not associated with improvements in cognition (214). Nonetheless, the interest in reducing oxidative stress in the brain is justified as a treatment approach because this type of injury could, at the very least, serve as a cofactor mediating AD progression. Potential approaches to reduce oxidative stress include the use of anti-oxidants, anti-inflammatory agents, radical scavengers, transition metal chelators, and non-vitamin anti-oxidant polyphenols.

7.5.1. Non-steroidal anti-inflammatory drugs (NSAIDs)—Epidemiologic studies demonstrated an apparently reduced risk of developing AD in ApoE∈4+ subjects that had been treated chronically with NSAIDs. Therefore, it was proposed that NSAIDs might be effective for treating AD, or preventing AD development in patients with MCI (136, 215–218). These concepts are supported by the known neuro-inflammatory responses that occur early in the course of AD, and contribute to AβPP-Aβ deposition (219). In addition, experimentally, neuro-inflammation leads to recruitment and activation of microglia and astrocytes, which mediate AβPP-Aβ deposition (220). However, in clinical trials, selective cyclooxygenase-2 (COX-2) inhibitor drug therapy proved to be ineffective for treating AD (216, 217), or in protecting individuals with MCI from progressing toward AD (217). Therefore, it seems unlikely that this avenue of therapy will help to significantly modify the course of AD.

7.5.2. Radical scavengers—Epidemiological studies suggested that long-term treatment with vitamin E, estrogens, or 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors (statins) may either help prevent dementia, or improve clinical outcomes (194). Interest in the role of estrogens was inspired by the findings that, estrogens stimulate cognitive performance in animal models and, bio-available estrogen declines with aging (221, 222), A few clinical studies have shown limited, short-term benefits of estrogen therapy with regard to cognition (222), but other better controlled trials demonstrated that exogenous estrogen therapy does not improve dementia symptoms in women with AD, and instead, it increases dementia risk when estrogen treatment is begun after age 65 (223, 224). On the other hand, the recent evidence that estrogen receptor modulation therapy may improve cognition (221, 225) deserves further study.

Statins are HMG-CoA reductase inhibitors. HMG-CoA catalyzes the rate-limiting step in cholesterol biosynthesis. In AD, perturbations in cholesterol metabolism and transport contribute to AβPP-Aβ deposition and tau hyper-phosphorylation (226, 227), and cerebrovascular disease, which contributes to vascular dementia and AD progression, is

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associated with hypercholesterolemia. Statin therapy has been evaluated in several clinical trials. Meta-analysis of several large prospective clinical trials revealed no significant benefits of atorvastatin or simvastatin therapy in patients with dementia who had been treated for periods ranging from 26 to 72 weeks, despite significant reductions in serum low density lipoprotein (LDL) (228–231). Still, other studies showed significant reductions in incident dementia among statin users (232, 233). Experimental data suggest that statins may provide some degree of neuroprotection (234).

In an anti-inflammatory treatment prevention trial, despite a 67% reduction in hazard risk of incident AD in subjects treated with lipid-lowering drugs, the most significant findings were that HDL was positively correlated with mini-mental state examination (MMSE) performance, and while LDL cholesterol was negatively correlated with immediate and delayed recall (235). Limitations of this study include its relatively short duration of follow-up and the lack of distinction between vascular dementia and AD. However, the impact of statin therapy was most likely due to reduced severity of cerebrovascular disease, lessening its contribution to AD progression. Recent concerns over the use of statins to treat AD were raised by the findings that: 1) brain cholesterol levels are reduced in AD (227); 2) reductions in neuronal cholesterol lead to impaired insulin signaling and energy metabolism (110); and 3) cognitive impairment can occur with chronic statin use (236–239) and following its discontinuation, cognitive function may be restored (237, 239). Therefore, routine, “preventive” use of statin therapy, particularly in the elderly, should be re-evaluated (240) and perhaps avoided unless indicated for cardiovascular health. Moreover, future studies should assess risk for further cognitive impairment among individuals with AD who do not have hyperlipidemia or cerebrovascular disease.

7.5.3. Transition metal ion chelators—One hypothesis that remains viable is that transition metal ions, including Al (III), Fe (III), Zn (II), and Cu (II), cause neurotoxicity and neurodegeneration (241–243), including in the earliest stages of AD (244). Excess accumulation of transition metal ions promotes oxidative stress, apoptosis, and aggregation and fibrillarization of hyper-phosphorylated tau (245) and AβPP-Aβ42 (243, 246). Oxidative stress is mediated by the formation of hydroxyl radicals following interactions between iron and hydrogen peroxide. In AD, brain levels of free heme and hemin are significantly elevated (247), and probably contribute to neurodegeneration by inhibiting cholinergic function, altering AβPP-Aβ metabolism, binding to hyper-phosphorylated tau and promoting tau aggregation into paired-helical filaments, and inducing formation of free radicals (247).

Chelation therapy with compounds such as desferrioxamine, Feralex-G, or Clioquinol affords neuroprotection by preventing the aggregation and fibrillarization of AβPP-Aβ and tau, and reducing ROS production (245, 248–250). Correspondingly, Clioquinol chelation reduces AβPP-Aβ burden in transgenic mice (248, 249). In addition to its proposed direct anti-aggregation effects on AβPP-Aβ, chelation therapy could reduce AβPP-Aβ deposition by decreasing oxidative stress and ROS (134) caused by heme and heavy metals. Chelation therapy for AD was tested in a 2-year randomized placebo-controlled trial of twice daily injections of the trivalent chelator, desferrioxamine. The rates of performance decline in patients with probable AD slowed (251). However, in a later uncontrolled clinical trial of Clioquinol therapy, AD subjects showed only modest improvements (250). Only a few

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studies have linked chelation therapy to improved glucose utilization, energy metabolism, and insulin signaling in the brain. Nonetheless, the findings that chelation of zinc and iron prevents or attenuates streptozocin-, alloxan-, or ferritin-induced diabetes (252–254), and that desferrioxamine chelation of iron, and dietary restriction of iron increase glucose uptake and insulin signaling in hepatocytes (255, 256) are intriguing with respect to the roles of brain insulin resistance and metabolic dysfunction in the pathogenesis of AD and neurodegeneration. Since treatment with antioxidants, Vitamin E, Vitamin C, Heme oxygenase 1, or metal chelators prevents the neurotoxic effects of heme and hemin (257), and may also enhance insulin signaling and glucose utilization in the brain, heme-induced oxidative stress could potentially be targeted by anti-oxidant and chelation therapy to help restore cholinergic function, reduce fibrillarization of tau and AβPP-Aβ42, decrease oxidative stress, and improve energy metabolism in the brain.

Despite probable benefits, a major limitation of our current methods of chelation therapy is that delivery of drugs with high Fe (III) binding capacity to the CNS are suboptimal (258, 259). Another point is that liberal use of chelation therapy may deplete iron, which is needed to generate energy, and copper, manganese, and zinc, which participate in enzymatic pathways that protect cells from free radicals and reactive oxygen species through activation of superoxide dismutases I–III. To address these problems, new compounds have been developed and tested in pre-clinical models. For example, DP-109 is a lipophilic metal chelator that reduces cerebral AβPP-Aβ burden in Tg2576 transgenic mice (260). Another approach may be to conjugate chelators to nanoparticles that can cross the blood-brain barrier to chelate metal ions, and then exit to remove them (261–263). Recently, Nano-N2PY, a prototype nanoparticle-chelator conjugate was demonstrated to inhibit AβPP-Aβ aggregation and reduce AβPP-Aβ-associated cortical neuron toxicity in vivo (264). Another novel approach involved the development of site-activated multifunctional chelators, such as HLA20A, that become activated by binding and inhibiting acetylcholinesterase, resulting in the release of an active chelator that reduces AβPP-Aβ fibrillization and oxidative stress (265, 266). Along related lines, dual target-directed 1,3-diphenylurea derivatives seem capable of both inhibiting BACE1 and chelating metal ions (267).

7.5.4. Polyphenols—Epidemiological studies demonstrated relative protection from dementia, AD, and Parkinson's disease in populations that regularly consumed green tea or red wine (268). Resveratrol, 3.4',5-trihydroxy-trans-stilbene, is a natural polyphenol that is abundantly present in red wine and has antioxidant and neuroprotective activities. Grape seed extracts also contain resveratrol, and therefore provide neuroprotection (269, 270). Pharmacokinetic studies have affirmed that grape seed polyphenols abundantly distribute in the brain (271). The neuroprotective actions of resveratrol are mediated by enhancement of glutathione free radical scavenger activity (272, 273), and reduction in AβPP-Aβ levels (274) due to increased clearance via the proteasome (275) or autophagy and lysosomal degradation (276). Resveratrol also exerts cytoprotective effects by stimulating heme oxygenase, and modulating cellular resistance blood flow, injury, and inflammation (277). In addition, resveratrol and other polyphenols function as metal chelators, and thereby protect the brain from oxidative stress and ROS caused by accumulations of lead, iron, aluminum, zinc, and copper (278).

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One critical therapeutic effect of resveratrol is its ability to retard aging and protect against AD due to stimulation of the sirtuin protein, SIRT1 (279). Sirtuin genes promote longevity, and SIRT1-mediated deacetylase activity protects against AD-type neurodegeneration (280, 281). Mechanistically, SIRT1 functions by interfering with AβPP-Aβ peptide generation (280, 281), and SIRT1-activating molecules such as resveratrol, reduce neurodegeneration and prevent learning impairments in the p25 transgenic mouse model of AD, which is associated with tau hyper-phosphorylation and fibrillarization (282). Of note is that SIRT1 activation achieves the same effect as caloric restriction with respect to preventing aging and AD (283). Caloric restriction with weight loss is a well-established means of increasing insulin sensitivity (284).

The major green tea polyphenolic compound, epigallocatechin-3-gallate (EGCG), has neuroprotective actions similar to resveratrol. Studies have shown that EGCG: 1) mimics cellular effects of insulin, reducing gluconeogenesis and corresponding enzyme gene expression (285); 2) reduces AβPP-Aβ levels by enhancing cleavage and clearance of the C-terminal fragment of AβPP (286); 3) functions as an iron chelating and mitochondrial stabilization compound (287, 288). Moreover, clinical trials have demonstrated that EGCG has neuroprotective and anti-oxidant therapeutic effects in AD, as well as Parkinson's disease (286, 288). To circumvent problems related to dosing and CNS delivery, nanolipidica EGCG particles have been generated and already shown to improve brain distribution following oral administration (289).

8. CONCLUSIONS

Recent literature concerning the roles of brain insulin and IGF resistance and deficiency in the pathogenesis of AD, and the likely mediators of brain insulin/IGF resistance and deficiency is reviewed. Based on human and experimental animal model data generated in various laboratories and institutions, the common theme that ties together nearly all of the pathophysiological abnormalities in AD, from early to late stages, is insulin and IGF resistance. The attendant inhibition of insulin/IGF signaling leads to aberrant activation of kinases that lead to tau hyper-phosphorylation. Impairments in energy metabolism and glucose utilization have broad consequences due to increased oxidative stress, activation of pro-inflammatory cascades, and ROS generation, all of which promote aberrant AβPP expression and cleavage, AβPP-Aβ42 accumulation, and fibrillarization and misfolding of tau and AβPP-Aβ. Increased ROS causes electrophilic attacks on proteins, lipids, and nucleic acids, resulting in the formation of adducts that promote further structural and functional damage, oxidative stress, ubiquitination of proteins, targeting them for degradation. Insulin/IGF resistance impairs lipid metabolism, leading to disruption of myelin homeostasis. AD also results in white matter atrophy, myelin loss, and increased myelin breakdown with generation of potentially toxic sphingolipids, including ceramides. Neurotoxic ceramides promote insulin resistance, neuroinflammation, and oxidative stress. Finally, brain insulin/IGF resistance can also explain the frequent co-existence of cerebral microvascular disease, which substantially contributes to the neuropathology of AD. Given the multi-step/multi-tiered problems caused by or associated with brain insulin/IGF resistance, treatment approaches should target AD at multiple levels, and multiple targets over a prolonged period (290, 291), similar to our current approaches for treating

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malignancies. Future multi-modal therapies for AD should be directed at multiple levels of within the insulin/IGF signaling cascade, beginning with receptor sensitizers, agents to promote insulin synthesis and release, e.g. GLP-1, inhibitors of oxidative stress, radical formation, and metal ion accumulation, tau phosphorylating kinase modulators, and co-factors that support glucose utilization, mitochondrial function, and energy metabolism. If effective, these combined treatments will likely enhance neurotransmitter activity and availability, neuronal plasticity, and neuronal survival, which are needed to preserve cognitive function.

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Abbreviations

AD	Alzheimer's disease
ADDL	Amyloid-derived diffusible ligand
ApoE-?4	Apoliprotein E, ? 4 allele
AßPP	Amyloid beta precursor protein
AßPP-Aß	amyloid-beta fragment of amyloid beta precursor protein
BACE1	Beta secretase 1
CNS	Central nervous system
COX2	Cyclooxygenase-2
CSF	Cerebrospinal fluid
DIO	Diet induced obesity
EGCG	Epigallocatechin-3-gallate
ER	Endoplasmic reticulum
GLP-1	Glucagon-like peptide-1
GSK-3ß	Glycogen synthase kinase-3ß
HMG-CoA	3-Hydroxy-3-methyl-glutaryl-CoA
IGF	Insulin-like growth factor
LDL	Low density lipoprotein
MCI	Mild cognitive impairment
MMSE	Mini-mental state examination
MRI	Magnetic resonance imaging
NASH	Non-alcoholic steatohepatitis
NSAID	Non-steroidal anti-inflammatory drug

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PET	Positron emission tomography
PI3 kinase	Phosphoinositol-3-kinase
PPAR	Peroxisome proliferator-activated receptor
PS	Presenilin
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SIRT1	Sirtuin 1 gene or protein
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus

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Table 1

Therapeutic targeting of brain insulin resistance in Alzheimer's disease

Target	Agent	Mechanism of Action
Aβ42 accumulation and fibrillarization	Gamma secretase inhibitor drugs (Notch sparing); BACE1 inhibitors to reduce cleavage and production of toxic peptides	Reduces insulin resistance, enhances PI3K-Akt signaling; reduces GSK-3β activity resulting in decreased tau phosphorylation
Tau hyperphosphorylation	GSK-3β inhibitors and protein phosphatase 2A agonists	Reduces oxidative stress, helps restore insulin responsiveness
Insulin deficiency	Insulin therapy-intranasal Incretins, e.g. GLP-1 to stimulate insulin	Maintains survival and function of cells requiring insulin stimulation; supports glucose uptake, brain metabolism and neuronal plasticity; Decreases AβPP burden and tau hyperphosphorylation; Enhances cognition
Hyperglycemia	Antihyperglycemic agents-biguanides	Enhance glucose uptake and insulin receptor sensitivity
Insulin resistance	Insulin sensitizers, e.g. PPAR agonists	Enhance glucose uptake and insulin receptor sensitivity; anti-inflammatory and anti-oxidant properties
Oxidative stress and Neuro-inflammation	Anti-oxidants Radical scavengers Anti-inflammatory agents Transition metal chelators	Help restore insulin sensitivity and glucose utilization Reduce Aβ42 deposition Reduce Aβ42 and tau fibrillarization Reduce cytokine activation-mediated injury Supports microvascular function and cerebral perfusion

Abbreviations: BACE1=beta site AβPP cleaving enzyme 1; GLP-1=glucagon-like peptide-1; PPAR= peroxisome proliferator-activated receptor; PI3K= phosphoinositol-3- kinase; GSK-3β = glycogen synthase kinase 3β; AβPP= amyloid-β - precursor protein; Aβ 42=amyloid beta peptide-42 amino acids 1–42 cleavage product; IGF=insulin-like growth factor