

Insulin Resistance and Neurodegeneration: Progress Towards the Development of New Therapeutics for Alzheimer's Disease

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Abstract Alzheimer's disease (AD) should be regarded as a degenerative metabolic disease caused by brain insulin resistance and deficiency, and overlapping with the molecular, biochemical, pathophysiological, and metabolic dysfunctions in diabetes mellitus, non-alcoholic fatty liver disease, and metabolic syndrome. Although most of the diagnostic and therapeutic approaches over the past several decades have focused on amyloid-beta (A β 42) and aberrantly phosphorylated tau, which could be caused by consequences of brain insulin resistance, the broader array of pathologies including white matter atrophy with loss of myelinated fibrils and leukoariosis, non-A β 42 microvascular disease, dysregulated lipid metabolism, mitochondrial dysfunction, astrocytic gliosis, neuro-inflammation, and loss of synapses vis-à-vis growth of dystrophic neurites, is not readily accounted for by A β 42 accumulations, but could be explained by dysregulated insulin/IGF-1 signaling with attendant impairments in signal transduction and gene expression. This review covers the diverse range

of brain abnormalities in AD and discusses how insulins, incretins, and insulin sensitizers could be utilized to treat at different stages of neurodegeneration.

Key Points

Alzheimer's disease should be regarded as an insulin-resistance-mediated neurodegenerative disorder that has the same fundamental abnormalities that occur in diabetes mellitus, metabolic syndrome, and non-alcoholic fatty liver disease.

Contrary to popular perception, Alzheimer's disease is associated with a number of major abnormalities in the brain which are not attended to by diagnostic and therapeutic approaches that specifically target amyloid-beta and phospho-tau accumulation.

Disease remediation for Alzheimer's and probably many other neurodegenerative diseases should be approached by attacking underlying impairments in the actions of insulin and insulin-like growth factors. Orchestrating the repertoire of drugs that support their multifaceted functions in the brain by efficiently and safely delivering insulins (short-, long- and ultralong-acting forms), incretins, and insulin sensitizers for disease-stage intervention could slow or halt progression of neurodegeneration.

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1 Introduction

Alzheimer's disease (AD) is clinically manifested by progressive behavioral changes, loss of recent, i.e. short-term memory, declines in executive functions, and deficits

in cognition [1]. Through structured longitudinal neuropsychological assessments of memory, intellectual function, and language skills, a diagnosis of possible or probable AD can be rendered. However, higher levels of diagnostic accuracy can be achieved using laboratory tests such as paired cerebrospinal fluid (CSF) and serum assays of amyloid precursor protein-amyloid beta 1-42 peptide (A β 42) and phospho-tau (pTau231) [2, 3], and neuroimaging [1], particularly magnetic resonance imaging (MRI) of the brain [4, 5], functional MRI (fMRI), diffusion tensor imaging (DTI) [6], single-photon emission computed tomography (SPECT), positron emission tomography (PET), and magnetic resonance spectroscopy (MRS) [7, 8].

1.1 Characteristic Neuropathology

Typically, neurodegeneration begins before it becomes clinically manifested as the typical neuropathological changes are detectable by postmortem examination of asymptomatic individuals. The brain structures hit earliest by AD include medial temporal and orbitofrontal regions, which are linked to neuronal plasticity needed for learning and memory. Over time, neurodegeneration grows in severity and distribution, with initial involvement of corticolimbic structures, followed by progressive destruction of other regions within the cerebral hemispheres.

Neurodegeneration is manifested by atrophy of cortical, white matter, and medial temporal structures with loss of neurons and synaptic terminals, neuro-inflammation, reactive astrocytosis, micro-vascular disease, accumulations of hyper-phosphorylated tau (pTau)-containing cytoskeletal lesion, increased amyloid-beta (A β 42) deposits in plaques, vessels, and neurons, and increased ubiquitin immunoreactivity in degenerating neurons [9–11]. Aberrant phosphorylation of tau via inappropriate activation of kinases causes Tau fibrillization, aggregation, and ubiquitination, followed by the stress-activated unfolded protein response (UPR), and ultimately cell death. Insoluble, fibrillar aggregates of hyper-phosphorylated and ubiquitinated Tau produce characteristic paired-helical filaments (PHFs) that are detectable by transmission electron microscopy and immunohistochemical staining. PHFs are major components of neurofibrillary tangles, dystrophic neurites, and neuropil threads which are signature AD lesions [12].

A β 42 is a \sim 4 kD peptide generated by secretase cleavage of amyloid beta precursor protein (A β PP). Under normal circumstances, A β 42 is continuously cleared from the brain by transport into the general circulation [13]. In aging and AD, A β 42 accumulates in cortical and leptomeningeal vessel walls, cortical and sub-cortical perivascular spaces, and plaques, and as neurotoxic, oligomeric soluble diffusible ligands (ADDLs) [14, 15].

1.2 AD Pathologies Unrelated to A β 42 and pTau

Although a neuropathologic diagnosis of AD is rendered by assessing the distribution and abundance of neurofibrillary tangles and senile plaques [10], the features of neurodegeneration are far broader and include: neuronal loss; neuro-inflammation; gliosis; white matter degeneration; and vascular degeneration, particularly in white matter [16, 17]. In addition, impairments in brain metabolism (glucose and oxygen utilization), although recognized for decades and frequently assessed, has not been incorporated into the cluster AD biomarkers. Failure to consider these additional aspects of AD limits opportunity to fully understand the nature of disease and therapeutically target its underlying basis. For example, significant degenerative changes emerge in cerebral white matter and micro-vessels early in AD; these abnormalities can be more conspicuous than neurofibrillary tangles and plaques. Restricting therapeutic interventions to A β 42 and pTau accumulations would not attend to other major pathologies that impair function and worsen with AD severity.

2 Neuro-Inflammation

Inflammatory responses in brains with neurodegeneration have been recognized for years but only recently have gained renewed attention as potential mediators of AD. Neuro-inflammation refers to the presence of activated microglia and astrocytes which cause injury through expression and release of pro-inflammatory cytokines, chemokines, and complement, increased generation of membrane fatty acids, eicosanoids, lipid peroxidation products, and reactive oxygen and reactive nitrogen species [18–20].

2.1 Neuro-Inflammation as a Mediator of Neurodegeneration

Neuro-inflammation is an early and consistent feature of many neurodegenerative diseases, including AD. Increased expression of pro-inflammatory cytokines such as interleukin-1 β (IL-1 β), IL-6, interferon-gamma, and macrophage migration inhibitory factor in the vicinities of A β 42 plaques supports the concept that neuro-inflammation is an important mediator or propagator of AD neurodegeneration [21, 22]. In addition, neuro-inflammation promotes neuronal injury and cholinergic dysfunction [23]. Downstream effects include oxidative stress with increased production of reactive oxygen and reactive nitrogen species, which can damage nerve terminals, causing synaptic dysfunction and attendant cognitive impairment [19]. Furthermore, since chronic inflammation is known to exacerbate insulin

resistance associated with systemic disease-states [24–28], neuro-inflammation could also have an important etiopathic role in the brain insulin and insulin-like growth factor-1 (IGF-1) resistances that occur in AD [29–34] and Parkinson's disease [35]. Furthermore, inflammation has inhibitory effects on incretin (orexin) expression and function, while reduced insulin resistance afforded by activation of incretin signaling inhibits pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- α) [36].

2.2 Role of Insulin Resistance in Neuro-Inflammation

Despite compelling evidence for a possible causal role of neuro-inflammation in neurodegeneration, its common presence in many other central nervous system (CNS) diseases including multiple sclerosis, malignant brain tumors, infections, traumatic injury, ischemic injury and stroke, perinatal leukoencephalopathy, and toxic-metabolic disorders suggests that such responses may be reactive rather than causal. In that regard, neuro-inflammation may produce secondary bystander injury rather than operate as the primary driver of neurodegeneration. In humans with peripheral insulin resistance diseases, including diabetes mellitus and metabolic syndrome, cognitive impairment and AD are partly driven by brain insulin resistance, together with neuro-inflammation and vasculopathy [37–39].

One of the brain abnormalities in AD that can be linked to both insulin resistance and neuroinflammation is down-regulation of peroxisome proliferator activator receptor (PPAR) delta [40]. In brain, PPAR-delta is the most abundantly expressed of the three isoforms of PPAR nuclear hormone receptors (alpha, beta/delta, and gamma) [41]. PPARs play critical roles in modulating insulin-stimulated gene expression in response to signals transmitted from surface membranes [42]. However, in addition to their insulin sensitizing actions, ligand activation of PPARs has potent anti-inflammatory effects [42–44]. The findings that, (1) PPAR-delta expression is reduced in AD brains [40]; (2) experimental depletion of PPAR-delta increases neuro-inflammation, astrogliosis, oxidative stress, A β 42 deposition, and PHF tau [45]; (3) PPAR-delta agonists are neuroprotective [46]; and (4) PPAR-delta agonists reduce neuro-inflammation and A β 42 deposition [44, 47, 48], convincingly support the notion that impairments in insulin signaling could account for many major abnormalities in AD, including neuro-inflammation. However, the fact that neuro-inflammation exacerbates insulin resistance, neurotoxic and oxidation-mediated cell death, gliosis, A β 42 toxicity, and PHF pathology means that the association between insulin resistance and neuro-

inflammation is tight. Another possible interpretation of this scenario is that insulin resistance and neuro-inflammatory pathologies co-conspire in a positive feedback loop to mediate neurodegeneration.

2.3 Oxidative Stress Contributes to Neurodegeneration

Neurodegeneration is consistently associated with oxidative stress resulting from increased generation of reactive oxygen and reactive nitrogen species [49]. These products exert their neurotoxic effects by reacting with macromolecules including lipids, nucleic acids (RNA and DNA), and proteins, causing their dysfunction [49, 50]. Oxidative damage occurs at very early stages of neurodegeneration [51] and has been linked to mitochondrial dysfunction in AD and other neurodegenerative diseases [52, 53]. Like neuro-inflammation, oxidative stress and free radical injury are not specific to neurodegeneration. Although oxidative stress can be caused by a broad range of exposures including hypoxia, ischemia, and insulin resistance, the resulting molecular, biochemical and cellular abnormalities overlap extensively with related pathologies in AD [54].

A long-standing hypothesis is that free radical stress and injury in AD are mediated by Fenton-type reactions [55] linked to excess iron accumulation in the brain [56]. This concept is supported by experimental evidence that impairments in iron metabolism increase levels of neuronal iron and lipid-peroxidation and protein carbonyl adducts in the brain [57]. In AD and many other neurodegenerative diseases, heme accumulation is regarded as a common and important mediator of oxidative stress [58]. In the brain, the deleterious effects of heme-induced free radical damage are broad and include inhibition of the muscarinic acetylcholine receptor [59], which likely contributes to cognitive decline in AD. Correspondingly, heme-associated impairments in muscarinic acetylcholine receptor function can be prevented by anti-oxidant treatment [59]. Heme oxygenases function by either dynamically or constitutively degrading heme to ferrous iron, carbon monoxide and biliverdin-IX-alpha. Heme oxygenases' anti-oxidant responses protect cells from injury [49] and activate the alpha7 nicotinic receptor [60]. Correspondingly, they exert their neuroprotective actions in part by inducing of heme-oxygenase 1 (HO-1) and reducing the levels of redox active iron in the brain.

Further evidence that iron accumulation and oxidative stress have etiopathic roles in AD stems from studies showing that deferoxamine treatment of P301L transgenic mice normalized performance in the radial arm water maze [61]. The P301L AD model is associated with phospho-Tau accumulations in the brain. Mechanistically, deferoxamine treatments reduced neuroinflammation, protein oxidation,

and GSK-3 β activation without altering brain levels of phospho-Tau [61]. Similarly, in the APP/PS1 mouse model, intranasal deferoxamine significantly improved performance in spatial learning and memory [62] while reducing GSK-3 β activation, oxidative stress, and levels of soluble A β 40 and A β 42 in the brain [63]. Despite these compelling insights, the ability to extend this logic to human diseases is limited by the uncommon and uncharacteristic nature of the experimental mouse genetic profiles relative to most human cases, and the fact that the causes of brain iron accumulation in these models are not obvious.

2.4 The Insulin Resistance, Oxidative Stress, Iron Overload, Neurodegeneration Network

Insulin resistance promotes oxidative stress by dysregulating carbohydrate and lipid metabolism, increasing GSK-3 β activation, and impairing cell survival/anti-apoptotic signaling, energy balance, mitochondrial function [54], and choline acetyltransferase and neurotrophin gene expression [64]. Brain insulin resistance is also associated with increased levels of phospho-Tau and A β 42 [54]. Iron accumulation occurs in both AD and type 2 diabetes mellitus [65]. Reducing iron load in the body enhances glycemic control in type 2 diabetes [65], just as deferoxamine treatment reverses or prevents AD-type abnormalities in experimental models [62, 63]. Paradoxically, HO-1 expression is substantially elevated in AD brains [66] and peripheral blood [67, 68]. Since HO-1 degrades heme, the up-regulated expression in AD suggests that endogenous neuroprotective mechanisms may become activated as a compensatory response to neurodegeneration. However, this explanation has been called into question by studies showing that in postmortem brains of patients with AD or mild cognitive impairment (MCI), HO-1 protein is post-translationally modified by serine phosphorylation, which increases its activity, and lipid peroxidation adducts, which would impair its function [69]. Thus, it is uncertain whether the aberrantly elevated levels of HO-1 in AD brains represent responses to neurodegeneration or oxidative damage and attendant inhibition of enzyme activity.

The findings in several studies that various aspects of neurodegeneration were abrogated by reducing heme make it difficult to refute the argument that neurodegeneration in insulin resistance diseases is mediated by dysregulation of iron metabolism, oxidative stress, and free radical damage [65, 68]. However, further exploration of this concept was enabled by review of neuro-cognitive abnormalities associated with genetic disorders of iron metabolism that lead to iron overload. Of particular interest is that hemochromatosis has been linked to glucose intolerance, insulin resistance, cognitive-motor impairments, and neurodegeneration [70–73], and studies have shown that the glucose

intolerance and insulin resistance improve with iron chelation therapy [74]. Unfortunately, these observations are also not entirely conclusive since people with hemochromatosis also have liver disease, and hepatic dysfunction can also cause cognitive-motor deficits and neurodegeneration.

Further studies addressed the same question using transgenic mouse models of hemochromatosis (HFE). One study found no evidence to support a direct and causal role for dysregulated iron metabolism in the pathogenesis of AD since the associated alterations in brain mRNA levels did not confer increased risk for AD-type neurodegeneration [75]. Additionally relevant findings in HFE models were that, (1) brain iron accumulations were most abundant in regions that regulate motor rather than cognitive functions; and (2) HFE hemochromatosis gene expression was mainly localized in choroid plexus epithelial cells, vascular endothelial cells, and ependymal lining cells rather than neurons and glia [70]. Despite early studies demonstrating probable links between the mutant hemochromatosis gene (HFE H63D) and increased risk for AD [76], other groups observed equivocal associations [77], and a later meta-analysis revealed that mutant HFE (H63D) most likely plays a protective role in reducing AD risk [78]. Additional research is needed to better understand how dysregulated iron metabolism contributes to neurodegeneration and cognitive impairment. One consideration is that iron accumulation may impair mitochondrial function and thereby cause oxidative stress and mitochondrial DNA damage, and metabolic dysfunction [79–82]. Mitochondrial DNA damage and dysfunction are well-recognized features of AD [53, 83] and other neurodegenerative diseases [84].

3 Brain Metabolic Dysfunction in AD

3.1 Deficits in Brain Glucose Utilization

The constellation of progressive neuropathological abnormalities in AD illustrates the need to conceptualize pathogenic mechanisms in ways that accommodate all aspects of disease rather than focus on just neurofibrillary tangles and senile plaques. The fact that most aspects of AD are fairly consistent from case to case suggests that the underlying basis of the seemingly unrelated pathologies may be shared. Deficits in brain energy metabolism, particularly with respect to glucose utilization in AD have been recognized for years. PET imaging with 18F-fluorodeoxyglucose (18F-FDG) is the standard approach for detecting early impairments in brain glucose metabolism [85, 86]. The most significant finding across multiple

studies is that AD is associated with global reductions in brain glucose metabolism relative to normal healthy control brains [87–90].

3.2 Insulin Functions in the Brain

Insulin and insulin-like growth factor, type 1 (IGF-1) polypeptides (growth factors) and receptors are expressed in the brain, most abundantly in regions that are most vulnerable to AD neurodegeneration [91]. Insulin regulates neuronal and oligodendroglial cell survival and neuronal plasticity [91, 92]. Experimental models have shown that brain insulin resistance or deficiency impairs learning and memory [64]. In early or intermediate stages of AD, brain and CSF levels of insulin are decreased [34], while A β 42 and advanced glycation end-products are increased [34, 54, 93]. High levels of A β 42 in brain and CSF are associated with low levels in serum due to decreased clearance [94]. Insulin administration improves working memory and cognition [95–98] and enhances A β 42 clearance from the brain [98].

3.3 Primary Brain Insulin and IGF Deficiency and Resistance in AD—Type 3 Diabetes

To validate the roles of insulin and IGF deficiencies and resistances in AD, human postmortem brains with different Braak stage severities of AD were used to measure expression levels of the corresponding trophic factors and receptors, ligand-receptor binding, and constitutive activation of downstream signaling [31, 99, 100]. Those investigations revealed significant AD stage-dependent declines in the expression of molecules needed to relay insulin and IGF-1 signaling including ligands, receptors and insulin-receptor substrate, type 1 (IRS-1), reduced insulin and IGF-1 binding to their cognate receptors, impairments in signaling through PI3K-Akt pathways needed for neuronal survival, plasticity, and metabolism, together with increased GSK-3 β activation [31, 99, 100]. Of further significance was the finding that impairments in brain insulin, IGF-1, and IGF-2 signaling mechanisms were correlated with reduced expression of choline acetyltransferase, which is needed to generate acetylcholine [31, 99, 100]. Subsequent studies confirmed that insulin and IGF-1 resistance [101] and impaired signaling through IRS proteins with attendant increased activation of GSK-3 β and suppression of PI3K-Akt [32] were fundamental features of AD in human brains.

The concept that brain insulin/IGF resistance and deficiency have significant roles in the pathogenesis of AD is supported by data showing that in the early stages of disease, CSF levels of insulin, IGF-1, nerve growth factor, and glial-derived neurotrophic factor levels were significantly

decreased while neuroinflammatory indices were increased relative to aged controls [34]. That study was highly significant because a postmortem diagnosis of AD was confirmed in all patients [34]. Together, these observations suggest that besides pTau and A β 42, biomarkers of brain metabolic and neurotrophin dysfunction should be included in CSF panels designed to aid in early detection of AD.

Because the human AD-associated abnormalities in insulin and IGF-1 signaling are highly reminiscent of what occurs in both type 1 (T1DM) and type 2 diabetes mellitus (T2DM), yet they selectively involve the brain, we coined the term ‘type 3 diabetes’ [99]. The objective was to convey the concept that AD is a brain form of diabetes in which both ligand (insulin and IGF-1) deficiencies and receptor resistances account for functional impairments in activating downstream signaling pathways. In addition to the deficits in insulin and IGF-1 signaling, cognitive impairment and AD are associated with reduced sensitivity (resistance) or ligand deficiencies pertaining to leptin and neurotrophins [34, 102, 103], and therapeutic responsiveness to incretins [104–106]; these abnormalities also occur in obesity, T2DM and other insulin-resistance diseases [107–113]. Therefore, in both type 3 diabetes and peripheral insulin resistance diseases, the mediators and correlates of metabolic dysfunction extend beyond impairments in insulin and IGF-1 signaling and more broadly include deficits in neurotrophin functions. For ‘type 3 diabetes’, although we hypothesized that the brain is the main target of metabolic dysfunction, since none of the subjects in our initial studies had clinical evidence of peripheral insulin resistance, emerging evidence suggests that the CNS regulates glucose metabolism in the body [114, 115] and that CNS impairments in metabolic signaling may drive obesity and peripheral insulin resistance [116–119]. Altogether, these concepts point toward the use of insulin and/or insulin sensitizer drugs for remediating brain diabetes early in the course of disease to prevent its progression and potential precipitation or exacerbation of systemic insulin resistance diseases.

3.4 Secondary Systemic Insulin Resistance Diseases and Cognitive Impairment

Analysis of epidemiological trends over several decades shows that the rates of AD increased sharply within all age groups, 50 years and above [120]. Parallel trends occurred for diabetes mellitus [120], suggesting that the underlying factors might be related. Equally important, the rapid shifts in disease prevalence correspond with effects of exposures rather than genetic factors. Correspondingly, data generated from multiple laboratories and institutions have shown that overweight or obese people and diabetics are at increased risk for developing cognitive impairment and

dementia [121–125]. Furthermore, individuals with inadequately controlled T1DM and T2DM also have higher rates of cognitive impairment [126–131] and a two-fold or greater risk of developing AD relative to people without diabetes [132]. Other studies have linked various forms of peripheral insulin resistance [133, 134] including pre-diabetes [127], metabolic syndrome [135], high fat diet-induced obesity [136, 137], and non-alcoholic fatty liver disease [138–140] to AD-type pathology and cognitive decline. Finally, multivariate analysis of a late onset AD international, multicenter cohort identified gene clusters associated with inflammation, diabetes, and obesity as pathologic processes linked to neurodegeneration [141].

In light of the evidence that various peripheral insulin resistance diseases can negatively impact brain structure and function and cause brain insulin resistance, it must be acknowledged that cognitive impairment and AD-type neurodegeneration can emerge either as primary or secondary CNS disease processes. In other words, ‘type 3 diabetes’ can arise in isolation (primary) with selective involvement of the brain, or as a consequence of systemic insulin resistance (secondary) due to obesity, diabetes mellitus, non-alcoholic fatty liver disease, or metabolic syndrome. Yet a third way to conceptualize the problem is to regard insulin resistance diseases as one process that can afflict one or multiple organs and tissues in the same way that atherosclerosis can target one or more vessels and produce distinct manifestations of disease. Importantly, the explanation for the rapid increase in rates of cognitive impairment and AD, even adjusting for age, probably is rooted in the parallel epidemics of obesity and other insulin resistance diseases rather than genetics per se. The good news is that the exposure-induced excesses in rates of neurodegeneration are probably preventable and treatable. The strategies are likely to be similar to those used and continuously under development to manage diabetes mellitus.

4 Therapeutic Strategies for Abrogating Brain Insulin Deficiency and Insulin Resistance in AD

4.1 Rational Therapeutic Options

AD neurodegeneration is associated with energy imbalance, dysregulated lipid and carbohydrate metabolism, cytokine-mediated inflammation, increased oxidative and other types of cellular stresses, on-going cell death, and vascular degeneration. The finding that these abnormalities are also present in T2DM, metabolic syndrome, and non-alcoholic fatty liver disease supports the concept that insulin-resistance diseases are all inter-related, could have the same root causes, and may be managed by similar if not

identical therapeutic strategies. Therefore, in designing treatment approaches, it would be prudent to remain mindful of the full range of molecular and cellular pathologies that must be addressed, and determine if the treatment responses are short-term or long-term, cell- or tissue-type specific, and broadly evident across different aspects of disease. Furthermore, non-invasive approaches are needed to assess and monitor the impact of various treatments on each component of neurodegeneration.

Regarding AD, any drug that can enhance brain glucose utilization and insulin signaling through the PI3K-Akt pathway, and thereby support neuronal survival, plasticity, and metabolism, should be regarded as a first-line therapeutic agent. Insulins should be given high-level consideration because besides stimulating insulin pathways, inflammation, cellular stress and neurotransmitter deficits are responsive to insulin. In contrast, anti-inflammatory agents, anti-oxidants and cholinesterase inhibitor drugs have narrower targeted effects, although they should be included with multi-pronged therapeutic regimens. Most of the chronic and progressive abnormalities, including white matter and vascular degeneration, can be attributed at least in part to brain insulin resistance; therefore, those aspects of AD should also respond to insulin and/or insulin sensitizers. Therapeutic options for treating AD as a metabolic disorder can be grouped under three headings: lifestyle changes, anti-inflammatory/anti-oxidant measures, and insulin signaling support.

4.2 Lifestyle Interventions

Lifestyle measures, including aerobic physical exercise, weight training and adopting a healthful diet are established strategies for lowering disease risk and severity in states of insulin resistance, including cognitive impairment and AD, and particularly in their preclinical and early stages [142, 143]. A meta-analysis study showed that reduced rates of physical exercise increase risk for developing AD [144]. This suggests that, in addition to protecting against cardiovascular disease, diabetes, obesity, and hypertension, healthful diets and regular physical exercise are neuroprotective and guard against mild cognitive impairment and AD [97, 145], and also positively impact neuronal plasticity [146]. Epidemiological data further suggest that the “Mediterranean diet” which is rich in fruits, vegetables and extra virgin olive oil, provides neuroprotection with aging [147], and that tight regulation of glycemia in diabetics helps preserve cognitive function [148]. In contrast, diets rich in simple sugars, particularly fructose, increase rates of T2DM, which in turn, enhances risk for AD [149]. Smoking is yet another avoidable risk factor for AD neurodegeneration as it increases neuro-inflammation, tau phosphorylation and A β 42 deposition

[150]. Other potential exposure-mediated causes of neurodegeneration linked to insulin resistance include neurotoxins [151], particulate matter present in polluted air [152, 153], and nitrosamines incorporated into processed and preserved foods and tobacco [154–158].

Nearly all protective lifestyle measures drive the body toward reducing insulin resistance, whereas accelerators of aging and cognitive impairment worsen insulin responsiveness. Aging is the dominant risk factor for cognitive impairment and neurodegeneration, including AD. Insulin resistance increases with aging. Lifestyle measures can reduce aging-associated insulin resistance. The protective effects of caloric restriction on aging demonstrated in earlier studies were likely due to concomitant reductions in insulin resistance. Therefore, lifestyle measures that preserve insulin responsiveness would likely protect against cognitive impairment and neurodegeneration [159]. From a public health perspective, although adopting healthy active lifestyles is the most logical and economically feasible approach to resolving the insulin resistance diseases epidemic, compliance has proven stubbornly difficult to sustain over prolonged periods. An additional consideration is whether lifestyle measures would even have significant neuroprotective effects in the intermediate or late stages of AD. If not, more definitive therapeutic strategies must be considered.

4.3 Anti-Inflammatory/Anti-Oxidant Agents

Epidemiological studies suggested that individuals who were chronically maintained on anti-inflammatory or anti-oxidant drugs for unrelated conditions had lower risks for developing cognitive impairment and AD [160]. Moreover, pre-clinical studies provided encouraging results showing that anti-inflammatory agents decreased neurofibrillary tangle burden [161, 162], tau phosphorylation [163], neurobehavioral (memory) deficits [164], A β 42 burden [165, 166], synaptic degeneration [48, 167, 168], and mitochondrial dysfunction [169]. Therefore, anti-oxidants with neuroprotective actions may be beneficial in the treatment of neurodegeneration, including AD [170, 171].

Curcumin has received considerable attention as a natural anti-oxidant and anti-inflammatory agent for treating AD due to its inhibitory effects on A β 42 deposition, A β 42 aggregation, and Tau phosphorylation, and positive effects on neurobehavioral function in preclinical AD models [166]. Other anti-oxidants and anti-inflammatory agents that may provide neuroprotection for AD include alpha-lipoic acid [172–174], Vitamin E [175, 176], resveratrol [170], phytonutrients [177], cyclooxygenase 2 inhibitors [178], Ginkgo [179], and melatonin [180]. However, thus far, formal clinical trials designed to treat or prevent AD by targeting neuro-inflammation and oxidative stress [181, 182] have yielded disappointing results

with respect to neuroprotection and preservation of cognitive function [166, 168, 183–185]. On the other hand, since neuro-inflammation emerges early and in pre-symptomatic stages of AD [186], relatively delayed treatment may not be effective because the peak period of related injury would have passed. The same phenomenon may hold with respect to A β 42 accumulations. Although clinical trials designed to remove plaques and increase A β 42 clearance failed to restore cognitive function, prevent cognitive decline, and reduce critical AD dementia-associated neuropathological abnormalities such as neuropil threads, dystrophic neurites, and neurofibrillary tangles [187–190], in order for this mode of therapy to be effective, it may have to be administered early, i.e. within the pre-symptomatic stages of disease. The same concept may hold with respect to therapeutic targeting of neuro-inflammation and oxidative stress [186] to prevent, reduce severity, or slow the rate of AD neurodegeneration. In support of this concept, in a recent publication of a randomized clinical pilot study, combined early intervention with omega-3 fatty acids, aerobic exercise, and cognitive stimulation significantly reduced progression of frontal, parietal and cingulate cortex atrophy in subjects with mild cognitive impairment [191].

4.4 Insulins

Insulin polypeptide has 51 amino acids and a molecular weight of 5808 Daltons. Insulin is first synthesized as a pre-hormone in which its signal peptide directs the protein to the ER for cleavage and subsequent formation of proinsulin. Folding, with the addition of three disulfide bonds, and subsequent enzymatic processing by prohormone convertases and carboxypeptidase E in the trans-Golgi network releases disulfide bond-linked A- and B-chains of insulin. Mature insulin is stored in mature granules as an inactive hexamer. Active monomeric insulin is released on demand in response to elevated blood glucose and food intake. In T1DM, insulin production is reduced or absent due to auto-immune destruction of the pancreatic islet beta cells. In T2DM, insulin production is elevated due to insulin receptor resistance in target organs, including skeletal muscle and adipose tissue. Higher levels of insulin are needed to achieve cellular responses to dietary glucose and energy metabolism. In addition, as T2DM progresses, states of insulin deficiency can emerge, further increasing the need for insulin therapy.

4.4.1 Physiological and Therapeutic Effects of Brain Insulin and IGF-1: Rationale for Insulin/IGF-1 Therapy in Neurodegenerative Diseases

In addition to stimulating glucose metabolism, insulin and IGF-1 support neuronal and oligodendroglial cell survival

[91, 92, 192], abundance and integrity of synapses [193], synaptic plasticity [91, 92, 193], and working memory and cognition [64, 95–98]. Other mechanistic actions of insulin that pertain to its potential use in targeting neurodegeneration include its anti-inflammatory effects [194], enhancement of A β 42 clearance from the brain [98, 195], and stimulation of brain energy metabolism [196, 197], cerebral blood flow, including to regions damaged in AD [198], and acetylcholine production [196]. It is noteworthy that insulin enhancement of A β 42 clearance was found not to be associated with altered expression of insulin degrading enzyme [195], which degrades both A β 42 and insulin [199], and therefore other mechanisms must be involved.

4.4.2 Pharmacokinetics of Insulins used for Therapy

Insulins vary with respect to their onsets of action, which correlate with the time interval required for their detection in peripheral blood after injection, peak periods of therapeutic response, i.e. maximum effectiveness in lowering blood glucose, and duration of action (time period of detection in peripheral blood). In addition, insulin's strength, conveyed in international units (U), ranges from 20 to 500, although the most common human dosage is 100 U. The fastest acting insulins are termed 'rapid-acting'. They are detectable in peripheral blood within 15 min of injection; their levels peak within 1 h; and blood levels are sustained for 2–4 h. Regular insulins are similar to natural pancreatic islet-derived insulin as they are short acting, detectable in peripheral blood 30 min after injection, with peak blood levels achieved within 2 or 3 h, and a therapeutic window that lasts 3–6 h.

Newer synthetic or recombinant insulins tend to have longer half-lives, later peak periods of maximum strength for lowering blood glucose, and longer durations of action relative to rapid- and short-acting insulins, and thus their therapeutic windows are considerably broader than with rapid- and short-acting insulins. Intermediate-acting insulins are detectable in peripheral blood 2–4 h after injection, produce peak levels 4 and 12 h later, and their therapeutic effects are sustained for 12–18 h. Long-acting insulins produce relatively stable peripheral blood insulin levels over a 24-h period, enabling once-per-day treatments. Finally, inhaled insulins were developed to administer rapid-acting insulin after meals and avoid additional injections in T1DM or T2DM patients who were already being managed with long-acting insulin. Inhaled insulin's effects are evident within 12–15 min and peak by 30 min. An advantage of this approach is that the "piggy backed" inhaled insulin has very short-term effects as it is not detectable 3 h after administration.

4.5 Insulin Therapy, Including Intranasal Delivery for Cognitive Impairment and AD

The brain needs insulin to support metabolism, neuronal survival, synaptic plasticity, myelin maintenance, growth and repair, and neuroprotection. Insulin deficiency and resistance emerge early in AD, and the resulting molecular, pathological, and biochemical abnormalities are essentially indistinguishable from the effects of other insulin resistance diseases such as diabetes mellitus and metabolic syndrome. This concept led to the term, 'type 3 diabetes' which conveys that the underlying problems in AD can be explained as a brain form of diabetes, and therefore, the therapeutic interventions could be the same or closely related. Insulin can be administered subcutaneous, transdermal, oral, sublingual, buccal, rectal, vaginal, intramuscular, intraperitoneal, or intranasal. Since insulin normally crosses the blood–brain barrier, systemic administration by various routes can modulate brain metabolism. Furthermore, in AD, compromise of the blood–barrier renders the brain even more accessible to insulin delivery from the periphery circulation.

Although clinical and experimental evidence suggests that insulin could be used to remediate brain metabolic dysfunction in AD, concerns about using peripherally injected insulin to treat the brain include off-target systemic effects such as hypoglycemia, and uncertainty about the efficiency of drug delivery across the blood–brain barrier. Intranasal delivery provides a realistic solution to these problems because with this non-invasive approach, insulin and other neurotrophins can enter the CNS and bypass the blood–brain barrier [96, 200, 201] while avoiding systemic effects. In contrast to inhalation, intranasal administration efficiently delivers drugs to ventromedial corticolimbic structures in the brain via olfactory and trigeminal nerves innervating the nasal cavity (olfactory) mucosa [202]. Due to connections with corticolimbic structures, intranasal insulin can be used to treat the most vulnerable targets of AD. Intranasal delivery approaches provide virtually unrestricted transfer of therapeutic compounds across the blood–brain barrier to the brain or CSF for disease-specific targeting at high levels of safety [200, 201].

4.6 Clinical Trials of Insulin Therapy for Cognitive Impairment and Early AD

A number of studies have demonstrated that insulin administration improves cognition and brain energy metabolism in people with mild cognitive impairment or early AD. In addition, insulin enhances clearance of A β 42, decreases activity of kinases that promote tau hyperphosphorylation, and enhances signaling through pathways

needed for synaptic plasticity [92, 203–205]. Furthermore, results from several clinical trials demonstrated that intranasal insulin improves working memory and cognition in individuals with mild cognitive impairment or early AD [98]. However, such responses are not fully generalizable as they appear to have been modulated by genetic background, particularly APOE- ϵ 4 genotype. APOE- ϵ 4 is the most prevalent genetic risk factor for AD and is present in 18–20% of the population. APOE- ϵ 4-negative subjects were reported to exhibit greater insulin-mediated improvements in cognition [203, 206, 207] while APOE- ϵ 4+ individuals either had no significant responses or their manifestations of AD worsened [207].

After a series of small trials, the multicenter 12-month SNIFF trial was conducted to examine responses to intranasal long-acting insulin (detemir) in subjects with amnesic mild cognitive impairment or probable mild AD [208]. Intranasal detemir improved cognition, verbal and visuospatial memory, and activities of daily living. Responses were most robust in subjects with the worst baseline performances, and they were modulated with respect to APOE- ϵ 4 carrier status [208]. However, in contrast to the earlier study from the same group [207], the SNIFF trial results revealed that significant improvements in verbal memory occurred in APOE- ϵ 4 positive carriers whereas significant declines were associated with APOE- ϵ 4 negative status [208]. Conceivably, the discrepant findings were related to insufficient statistical power of the earlier clinical trials. Nonetheless, the findings in multiple studies provide ample evidence that insulin therapy, particularly via intranasal delivery, slows progression of cognitive impairment and AD, although the role of genetic factor regulation of treatment responsiveness requires further investigation. An additional caveat is that the data could reflect the need to go beyond monotherapy and extend the therapeutic targets to mediators of insulin resistance, as well as other abnormalities including neuroinflammation and deficits in neurotrophin and incretin signaling in AD.

4.6.1 Challenges Facing Intranasal Insulin Therapy for Cognitive Impairment and AD

Although cognitive impairment and AD can be treated with either systemic or intranasal insulin, proper administration of the latter has the potential to selectively target the brain with generally high levels of safety due to the low rates of off-target side effects such as hypoglycemia [96]. Furthermore, intranasal therapy avoids the need for multiple daily injections. Finally, as the priority dates of patents for intranasal agent delivery, including insulin to treat AD have expired (US5624898 A and US6313093 B1), opportunities exist for expanding this mode of therapy, including

to the use of long-acting insulins to address a pressing need due to the large number of patients with AD throughout the world.

Despite its compelling strengths, intranasal therapy faces several challenges. First, delivery protocols must be standardized and simplified to enable routine management by elderly individuals; otherwise dose variability will lead to suboptimum and inconsistent responses. A second concern is the need to avoid off-target effects due to inadvertent systemic delivery and attendant hypoglycemia. This concern is serious and potentially devastating, particularly in elderly patients because the brain regions damaged by hypoglycemia are the very ones that require treatment for AD. The third point is that therapeutic agents, including insulin, delivered via the intranasal route should be structurally stable, relatively resistant to degradation, and able to penetrate the nasal mucosa. Finally, the potential for developing nasal transport resistance and reduced absorbance could limit the effectiveness of intranasal therapy [96]. Therefore, to further the use of intranasal insulin and other neurotrophins to treat CNS diseases, improvements in delivery systems, means of monitoring CNS delivery and brain responses, and assessments of nasal transport resistance are needed. On the other hand, the emergence of newer, ultra-long-acting insulins with predictably sustained release and bioactivity profiles, together with substantial margins of safety and efficacy [209–211], could represent the next generation of insulin compounds for treating cognitive impairment and AD.

4.7 Incretins

Incretins, including glucose-dependent insulintropic polypeptide (GIP), glucagon-like peptide-1 (GLP-1), are metabolic hormones that signal reductions in blood glucose levels by stimulating insulin secretion, insulin gene expression, and pancreatic beta cell proliferation [212]. In addition, long-acting liraglutide was demonstrated to ameliorate impairments in insulin signaling in an AD mouse model (APP^{SWE}/PS1^{dE9}) by normalizing cell membrane distributions and localizations of the insulin receptor, reducing expression of pS(616) IRS-1, which inhibits downstream insulin signaling, neuroinflammation, and astrogliosis [213]. Incretin enhancement of nutrient-induced insulin release has potentially broad therapeutic applications, including for the treatment of cognitive impairment, osteoporosis, T2DM, and obesity [214, 215]. However, since GLP-1 and GIP are rapidly degraded by dipeptidyl peptidase-4 (DPP-4) following secretion by K and L cells of the gastrointestinal track [119, 212], they have minimal exogenous therapeutic utility. Instead, synthetic long-acting analogs with insulintropic activity, including liraglutide and Exendin-4, are more suitable for

in vivo experimentation and human clinical trials. Alternatively, inhibitors of DPP-4 could potentially be used to prolong the half-life of GLP-1 and GIP and regulate blood glucose in T2DM [107].

Although the effects of liraglutide could have been mediated by systemically increased insulin secretion, GLP-1 is expressed in brainstem neurons [216] that project widely throughout the CNS [217], and its receptors are expressed in ventral tegmental area, paraventricular nucleus and nucleus accumbens neurons [218] which receive projections from GLP-1 expressing brainstem neurons [218, 219]. The peripherally administered GLP-1 analog effects on food intake and body weight are likely mediated through CNS actions [220, 221], as these compounds can cross the blood–brain barrier [222, 223]. However, there is also evidence that CNS-mediated GLP-1 receptor activation has peripheral effects in regulating blood glucose [224], lipid metabolism [225], cardiovascular function [226].

In the CNS, incretins and incretin analogues are neuroprotective [227] because they enhance synaptic plasticity, cell proliferation, and memory, and they reduce A β 42 plaques, oxidative stress, neuro-inflammation, and gliosis without causing adverse cardiovascular effects [228–232]. In light of the significant and progressive diabetes-like impairments in insulin signaling that occur with increasing AD stage [31, 32, 54], translational and clinical research to determine if incretin therapy can be extended to AD and other neurodegenerative diseases has been conducted.

The long-lasting GIP incretin hormone analogue, D-Ala(2)GIP, was found to protect memory formation and synaptic plasticity, normalize proliferation of stem cells, and reduce A β 42 plaques and activation of microglia and astrocytes (neuroinflammation and oxidative stress) in the APP^{swe}/PS1 Δ E9 mouse model of AD [228]. In addition, A β 42-inhibition of insulin signaling in neuronal cells was reversed by treatment with a DPP-4 inhibitor [233]. Exendin-4 (Ex-4), an incretin mimetic long-acting GLP-1 receptor agonist approved for T2DM, has neurotrophic and neuroprotective activity in cellular and animal models of stroke, Alzheimer's and Parkinson's diseases [229–231]. Correspondingly, encouraging results were obtained from a small pilot study in which liraglutide was found to have modest neuroprotective effects manifested by improvements in brain glucose metabolism in subjects with AD [234].

One potential disadvantage of incretins is that they must be administered by injection and they must be long-acting to be effective for human therapy. Moreover, since brain insulin resistance worsens as AD progresses to intermediate and late stages, the therapeutic window for targeting AD with insulins may narrow and possibly vanish over time. Additional research is needed to determine if incretin

receptor resistance also develops with advancement of AD stage of neurodegeneration.

4.8 Metformin

The potential use of anti-diabetes drugs apart from insulins to manage cognitive impairment and AD is very exciting due to the large body of data from clinical trials and clinical experience. Evidence is emerging that cognitive function can be preserved by managing diabetes, including with metformin [132, 204, 235–237]. Thus far, just two major metformin clinical trial results have been published, one from Australia and the other from Singapore [132, 204]. However, the findings were somewhat contradictory. The Australian study reported an increased risk for cognitive impairment among patients with T2DM following long-term treatment with metformin [236], whereas the Singapore study showed that metformin provided neuroprotection in older adults with T2DM [238]. The confounding factor in the Australian study was that the adverse effects of metformin were largely due to concomitant Vitamin B12 deficiencies, which when corrected, abrogated the apparently detrimental effects of metformin. In a later independent study, metformin treatment of overweight or obese, previously untreated diabetics with amnesic mild cognitive impairment had a statistical trend for positive performance effects on the selective reminding test [239]. Given the widespread use of metformin and its potential effects on cognition, additional research including execution of a large multinational longitudinal study and meta-analysis of smaller studies are warranted.

4.9 Thiazolidinediones: Nuclear Hormone Receptor (Peroxisome-Proliferator Activated Receptor) Agonists

Peroxisome-proliferator activated receptors (PPARs) are nuclear hormone receptors of which there are three main types: alpha, beta/delta, and gamma. In addition, subtypes of PPAR-gamma have been identified [240]. Differential expression of one or more PPAR type and subtype enables relatively selective modulation of gene expression in tissues. Once activated, PPAR protein heterodimerizes with retinoid X receptor (RXR) and the complex then binds to target sequences that contain peroxisome proliferator hormone response elements within DNA promoters and function as transcription factors to regulate target gene expression, including in the brain [240]. Since PPARs have pivotal roles in regulating carbohydrate, protein, and lipid metabolism, as well as inflammatory responses [241–245], their agonists offer excellent opportunities for treating various aspects of brain diabetes while circumventing problems stemming from insulin resistance [46, 47]. In

addition, recent evidence suggests that PPAR agonists can also activate IGF-1-regulated pathways in the brain [47].

In one early but small clinical trial, PPAR-gamma agonist treatment of subjects with mild cognitive impairment or early AD was demonstrated to enhance cognitive function [246]. In a later study, responses to metformin, rosiglitazone and dual treatments were examined. The results indicated that rosiglitazone treatment of diabetics was more effective than metformin in stabilizing long-term cognitive function [247].

Pioglitazone is the second PPAR-gamma agonist to gain attention for potential treatment of AD. In preclinical models, pioglitazone was shown to restore deficits in synaptic transmission and enhance long-term potentiation [248], reduce cerebellar dysfunction [249], and restore dendritic spine densities and adaptive plasticity responses damaged by A β 42 [250]. Currently, in an ongoing Phase III clinical trial, low-dose pioglitazone is being tested to determine if it can delay the onset of MCI and its progression to AD in normal subjects [251]. Importantly, the experimental treatment dose is considerably lower and therefore less toxic than the one used to treat T2DM because dose optimization was achieved by determining the pioglitazone dose that was needed to increase oxygen consumption in the brain based on blood-oxygen-level-dependent contrast imaging with fMRI [251]. Correspondingly, in preclinical experiments, low doses of PPAR agonists proved to be more effective and less toxic than high doses for reversing or preventing AD pathologies in experimental models of sporadic AD [46, 47, 252].

Effective brain targeting to enhance brain insulin/IGF signaling and thereby slow or prevent neurodegeneration and cognitive impairment with PPAR agonists will most likely require the use of mainly PPAR-delta, followed by PPAR-gamma agonists since most of the PPARs expressed in brain are delta [41]. Furthermore, PPAR-delta agonists are neuroprotective [253, 254], they inhibit neuro-inflammation [44, 255], reduce A β 42 accumulation [44], support function in vascular endothelial [256] and smooth muscle [257] cells, promote oligodendrocyte maturation [258], which is needed for myelin maintenance, may negatively regulate CNS neuronal circuitry that drives obesity [259, 260], support cognitive function [261], and prevent neurodegeneration, including AD-type [262] in experimental models [46, 48]. However, since PPAR-gamma agonists also have neuroprotective effects, it may be beneficial to therapeutically target both PPAR-delta and PPAR-gamma for disease remediation in AD. In this regard, preclinical studies have shown that T3D-959, a novel hybrid PPAR-delta/PPAR-gamma agonist [263–265] can effectively restore cognitive function, integrity of temporal lobe/hippocampal structure, and insulin/IGF-1

sensitivity and inhibit neuro-inflammation in a sporadic model of AD [47, 48, 266]. PPAR delta/gamma agonists could be most effective in early to intermediate stages of AD, coinciding with emergence and progression of brain insulin/IGF-1 resistance, and either in concert or tandem with early insulin and/or incretin therapy for mild cognitive impairment and AD neurodegeneration.

5 Conclusions

AD should be regarded as a brain form of diabetes in which insulin resistance and deficiency develop either primarily in the brain, or due to systemic insulin resistance disease with secondary involvement of the brain. Nearly all pathologies in AD, including the typical A β 42 and phospho-tau containing, PHF-associated structural lesions, metabolic dysfunction, neuro-inflammation, cellular stress, synaptic disconnection with proliferation of dystrophic neurites (reflecting loss of neuronal plasticity), cell death, white matter atrophy and degeneration, and microvascular disease, could be attributed to impairments in insulin and IGF signaling. Therefore, apart from reducing burdens of A β 42 and pTau, therapeutic interventions must be designed to ameliorate the broader and multifaceted components of AD neurodegeneration. To that end, therapeutic interventions should include measures that increase insulin supply, enhance insulin/IGF-receptor responsiveness, and modulate downstream signaling through IRS and insulin/IGF target gene expression.

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