Review

Insulin and Alzheimer’s Disease: Untangling the Web

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Abstract. The recognition of Alzheimer’s disease (AD) as a heterogeneous disorder that results from incremental pathological changes in dynamic organismic systems is essential to move beyond the unidimensional approaches to prevention and therapy that have proven largely ineffective to date. Biological systems related to insulin metabolism are arguably the most critical regulators of longevity and corporeal aging. Our work has focused on identifying the relationship of the insulin network to brain aging, and determining the mechanisms through which insulin dysregulation promotes AD pathological processes. Candidate mechanisms include the effects of insulin on amyloid-β, cerebral glucose metabolism, vascular function, lipid metabolism, and inflammation/oxidative stress. It is likely that different nodes of the insulin network are perturbed for subgroups of AD patients, or that for some subgroups, pathways independent of insulin are critical pathogenetic factors. New methods from systems network analyses may help to identify these subgroups, which will be critical for devising tailored prevention and treatment strategies.

In the following review, we will provide a brief description of the role of insulin in normal brain function, and then focus more closely on recent evidence regarding the mechanisms through which disruption of that role may promote AD pathological processes. Finally, we will discuss the implications of this area for AD therapeutics and prevention.

Keywords: Alzheimer’s disease, diabetes, insulin, network analysis

INTRODUCTION

Late onset Alzheimer’s disease (AD) is a heterogeneous disorder resulting from the cumulative perturbation of multiple pathways. This realization has sparked interest in pathogenetic models that extend beyond a narrow focus on factors such as cholinergic deficiency or amyloid accumulation. Insulin resistance is a condition that affects multiple pathways of relevance to AD, and has been proposed to play a key role in its pathogenesis. The insulin resistance syndrome occurs when tissues become unresponsive to the effects of insulin and can selectively affect insulin’s actions on muscle, liver, adipose tissue, endothelium, or brain. It is typically accompanied by compensatory hyperinsulinemia in the periphery, which may have independent deleterious effects. For example, chronic hyperinsulinemia may downregulate insulin transport across the blood brain barrier, leading to reduced insulin levels in the central nervous system (CNS) [1]. Insulin resistance is thought to be a primary cause of metabolic syndrome, diabetes, hypertension, and cardiovascular disease. It has also been shown to increase the risk of AD, as well as vascular dementia. In the following review, we will provide a brief description of insulin’s role in normal brain function, and then focus more closely on recent evidence regarding the mechanisms...
through which disruption of that role may promote AD pathological processes. Finally, we will discuss the implications of this area for AD therapeutics and prevention.

INSULIN AND THE BRAIN

Insulin is a peptide secreted by pancreatic β-cells, whose peripheral effects are well known. Insulin also has multiple functions in the CNS. Although controversy exists as to whether insulin is synthesized in the adult brain, insulin is readily transported across the blood brain barrier by a saturable, receptor-mediated process [2–4]. Insulin receptors are located in the synapses of both astrocytes and neurons where insulin signaling contributes to synaptogenesis and synaptic remodeling [5–7]. High concentrations of insulin receptors occur in the olfactory bulb, cerebral cortex, and hippocampus [3, 8–10]. Substantial co-localization exists for insulin-containing neurons, insulin receptors, and glucose transporter isoforms 4 and 8 in hippocampus and medial temporal cortex, suggesting that insulin influences memory in part through insulin-stimulated glucose uptake [11]. Other insulin-related mechanisms have also been implicated in normal hippocampal functioning [12]. For example, insulin may modulate cell membrane expression of NMDA receptors [13], and thereby affect long-term potentiation (LTP) induction. Insulin also modulates CNS levels of neurotransmitters such as acetylcholine and norepinephrine that influence cognitive function [14, 15]. In recent work, intranasal insulin (INI) enhanced episodic and working memory in older adults [16]. Thus, insulin affects numerous mechanisms relating to neuronal activity and cognitive function supported by such activity.

INSULIN ABNORMALITIES AND AD PATHOLOGY

Hoyer and colleagues first identified a reduction in insulin receptors and signaling markers in the AD brain [17]. This initial finding has been confirmed and extended by other investigators, who have demonstrated reduced CSF insulin in patients with AD and mild cognitive impairment (MCI) [18, 19], and reduced insulin and IGF-I signaling with increasing AD pathology and cholinergic deficit [20]. Insulin has a close relationship with amyloid-β (Aβ), the toxic peptide produced by cleavage of the amyloid β protein precursor (AβPP) [7]. In AD, insoluble Aβ peptides deposit in brain parenchyma and vasculature. Soluble Aβ species, particularly oligomers of the 42 amino acid species (Aβ42), have synaptotoxic effects, possibly resulting in synapse loss, which is the earliest structural defect observed in AD [21]. Insulin reduces oligomer formation and protects against Aβ-induced synaptotoxicity and LTP disruption [22–24]. Interestingly, Aβ also regulates brain insulin signaling. Soluble Aβ binds to the insulin receptor and disrupts insulin signaling and LTP induction in mouse hippocampal slice preparations [25]. These effects could be prevented by exposing tissue to insulin prior to Aβ exposure. Insulin pre-treatment also prevented synthetic soluble Aβ oligomers from downregulating plasma membrane insulin receptors and reducing dendritic spines in primary hippocampal neurons [22].

Talbot and colleagues recently confirmed previous reports that a key signature of insulin resistance, the serine phosphorylation of insulin receptor substrate-1 at the 312, 616, or 636 sites (IRS-1 pSer312, 616, or 636) exists in AD brain in basal states [26], and extended these findings using ex vivo stimulation to provide evidence of functional insulin resistance in AD brain. Oligomeric plaque load was correlated with insulin receptor tyrosine phosphorylation (negatively) and levels of IRS-1 serine kinases (positively) in their sample of control, MCI, and AD cases. Importantly, higher levels of insulin resistance markers were associated with worse performance on tests of working and episodic memory in these patients, independent of the effects of oligomeric plaque and tangle load, suggesting that insulin signaling has a direct association with cognitive status.

Recent in vivo evidence that Aβ can interfere with brain insulin signaling was provided by Bomtm et al., who use a primate model in which adult cynomolgus monkeys received intracerebroventricular infusions of Aβ oligomers. They observed evidence of insulin resistance (increased IRS-1 pSer636 levels) in the hippocampi and temporal cortex of treated monkeys compared with a sham-operated monkey, along with elevated levels of pJNK which has been linked to IRS1 serine phosphorylation in diabetes and peripheral insulin resistance. Collectively, these findings suggest that soluble Aβ may induce CNS insulin resistance and synapse loss, and that correcting insulin abnormalities may prevent these pathological processes. Conversely, peripheral insulin resistance may also induce or exacerbate AD pathological processes in the brain. For example, inducing insulin resistance through high fat or high sucrose diets increases brain amyloid burden and memory impairment in AD mouse models [27, 28].
We recently demonstrated the effects of diet-induced metabolic syndrome on cerebrospinal fluid (CSF) Aβ in normal older adults and adults with MCI [29], a study that will be described in more detail in a later section [29]. A role for insulin has also been suggested for other AD pathology markers. Insulin inhibits phosphorylation of tau, through its regulation of glycogen synthase kinase 3β (GSK3β), a downstream target in the insulin signaling pathway [30].

**INSULIN RESISTANCE AND CEREBRAL GLUCOSE METABOLISM**

AD is characterized by a pattern of cerebral glucose hypometabolism thought to be due to synaptic dysfunction, which involves a network of brain regions known as the default mode network. Reduced metabolism in this network is observed years before the onset of clinical AD, and is also observed in adults at risk for AD by virtue of conditions such as APOE-e4 allele or presenilin-1 gene carriage, or midlife hypercholesterolemia. We recently reported that cognitively normal, never medicated insulin resistant adults also demonstrate hypometabolism in default mode network regions such as the posterior cingulate/precuneus using fluorodeoxyglucose postmortem emission tomography (FDG-PET), and that reduced metabolism was associated with subtle reductions in memory encoding (Fig. 1) [31]. Similar patterns have been reported with resting state fMRI for insulin resistant adults [32]. The longstanding FDG-PET finding of posterior cingulate/precuneus hypometabolism in AD has been hypothesized to be due to functional disconnection of the hippocampal formation, which in turn contributes to the memory deficits which characterize AD dementia. Similarly there are strong connections between the posterior cingulate/precuneus/parietal and prefrontal and superior temporal cortex, which may contribute to other aspects of cognitive impairment [33]. Taken together, these results suggest that increased insulin resistance may be a marker of AD risk that is associated with reduced cerebral glucose metabolism and subtle cognitive impairments at the earliest stage of disease, even before the onset of MCI.

**INSULIN RESISTANCE ASSOCIATIONS WITH VASCULAR FUNCTION, DYSLIPIDEMIA, AND INFLAMMATION**

Insulin resistance has many negative effects on vascular function which are directly related to impaired insulin action, or may be secondary to insulin resistance-induced dyslipidemia and inflammation. Insulin directly affects vasoactivity and hemodynamic functions, such as capillary recruitment, vasodilation, and regional blood flow. Hemodynamic and metabolic effects working in concert enhance energy substrate delivery [34]. Insulin normally increases NO-mediated vasodilation and regulates vasoconstriction via endothelin-1. Conversely, insulin resistance decreases NO and increases endothelin-1 activity, favoring vasoconstriction and reducing capillary recruitment. In turn, endothelial dysfunction reduces insulin transport, ultimately reducing capillary recruitment and microvascular blood flow. This exacerbates glucose and lipid abnormalities, and establishes a negative feedback loop between progressive endothelial dysfunction and increasing insulin resistance [34]. In brain, vasoconstriction and reduced capillary recruitment may interfere with functions of the neurovascular unit, the coordinated interaction of astrocyte, neuron, and endothelium which couples neural activity with increased blood flow.

Vascular dysfunction is often associated with dyslipidemia, which has also been identified as an AD risk factor. In a recent meta-analysis of 18 prospective studies examining the relationship of total cholesterol and risk for AD, mid-life total cholesterol levels were consistently associated with an increased risk of AD and all dementia, whereas no increased risk was observed for late-life total cholesterol [35]. Dyslipidemia is an important component of the insulin resistance syndrome; insulin is a primary regulator of lipid metabolism, stimulating lipogenesis and reducing lipolysis. Conversely insulin resistance leads to accelerated lipolysis and increased free fatty acid levels, leading to higher and more prolonged postprandial excursions of very low-density lipoprotein (VLDL) and other deleterious lipids. This tendency has important implications for AD pathological processes. Interactions among lipids, lipoproteins, and Aβ play a critical role in Aβ production and clearance. In rodents, increased peripheral VLDL secretion precedes Aβ deposition in brain [36], and high fat feeding increases brain amyloid burden [37]. The specific mechanisms through which lipids and lipoproteins affect Aβ production and clearance, and the manner in which insulin resistance impacts this process is an area of intense inquiry.

Vascular impairment and dyslipidemia are also associated with inflammation, a key factor in AD [38, 39]. Increased levels of cytokines and other inflammatory agents have been observed in the brains of AD patients.
For example, the inflammatory cytokine interleukin-6 (IL-6) is present in senile plaques, a hallmark of AD [40], and AD patients have elevated CSF concentrations of IL-6 and F2-Isoprostane, a biomarker of brain lipid peroxidation [41, 42]. Furthermore, in vitro and animal studies suggest that inflammation interacts with processing and deposition of Aβ [43]. In the periphery, insulin modulates many aspects of the inflammatory network. Anti-inflammatory effects are observed with low doses of insulin [44]; however, during long-term hyperinsulinemia or chronic inflammation, insulin may exacerbate the inflammatory response and increase markers of oxidative stress. In humans, plasma concentrations of C-reactive protein and the proinflammatory cytokines IL-1β, IL-6, and TNFα were increased synergistically when insulin was administered with the endotoxin lipopolysaccharide [44]. Insulin may also contribute to inflammatory responses in the CNS. We demonstrated that intravenous infusion of insulin to levels associated with insulin resistance increased CSF F2-Isoprostane and cytokine levels [45]. Insulin also increased plasma and CSF concentrations of Aβ42, changes that were significantly correlated with increased F2-Isoprostane and cytokine levels. These results demonstrate that hyperinsulinemia, at levels associated with insulin resistance, can elevate inflammatory markers and Aβ42 in the periphery and the CNS, which may increase the risk of AD.

SUMMARY AND FUTURE DIRECTIONS: SYSTEMS AND NETWORK APPROACHES

As is apparent from the above review, insulin dysregulation and AD may be linked via multiple pathways, with bidirectional relationships between periphery and CNS. In some subgroups, AD pathological processes may be driven from the periphery, as peripheral insulin resistance is induced by environmental factors such as unhealthy diet and physical inactivity that ultimately impact the CNS in vulnerable adults. In other subgroups, brain insulin resistance may be induced by AD pathological processes such as amyloid accumulation or oxidative stress, which may ultimately perturb peripheral metabolism. The nature of these associations may change over time as they are influenced by developmental, counterregulatory, and pharmacologic factors. Discerning these relationships and identifying the characteristics which define subgroups of at-risk adults for tailored treatment or prevention strategies is a complex undertaking that likely will require the application of network-based systems biology approaches. Rather than traditional approaches which relate individual genes or proteins to a certain disease phenotype, systems-based approaches investigate networks of related biological data simultaneously (Fig. 2). For example, subgroups of AD patients may be classified on the basis of the activity of the entire insulin signaling pathway rather than expression of individual genes or proteins. Common pathophysiological pathways underlying disease associations such as have been observed for AD, and insulin-resistance related conditions such as diabetes, hypertension, and cardiovascular disease can also be explored with systems approaches. Finally, treatment and prevention strategies aimed at correcting insulin dysregulation in AD are likely to involve multiple or pleiotropic agents that target different aspects of disease pathways, and the probabilistic efficacy of combinatorial strategies can be addressed through network analysis. In the next section, we describe approaches to therapy and prevention that may be beneficial to adults for whom insulin resistance is an AD-promoting factor.

INSULIN RESISTANCE-BASED APPROACHES TO AD PREVENTION AND THERAPY

Insulin sensitizers and insulinotropics

Given the relationship between insulin resistance and memory impairment, therapeutic strategies aimed...
at treating early type 2 diabetes (T2D) may also benefit adults with MCI or AD. Peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists improve insulin sensitivity, decreasing circulating insulin, and increasing insulin-mediated glucose uptake, with minimal risk of hypoglycemia [46]. PPAR-γ activity may also reduce both Aβ accumulation and inflammation and thereby protect against neurotoxicity [47–49]. PPAR-γ agonists inhibit Aβ-stimulated secretion of pro-inflammatory products and decreased oxidative stress in both in vitro and in vivo models [50, 51]. PPAR-γ agonists are thus attractive candidates for the treatment of insulin resistance and inflammation associated with early cognitive decline.

Despite a strong rationale to examine the effectiveness of PPAR-γ agonist treatment in persons with AD, results from human clinical trials have been mixed. One trial of rosiglitazone, a compound that binds with high affinity to PPAR-γ [52], in patients with amnestic MCI and early AD resulted in improved performance on selective cognitive functions and a more favorable plasma Aβ40/42 ratio [53]. A larger six-month trial failed to yield overall cognitive benefit, although improvement was noted in subjects without an APOE ε4 allele on a task of general cognitive function at the highest dose [54]. Subsequent Phase III clinical trials, however, failed to show any cognitive improvements in patients with mild to moderate AD, regardless of genetic status [55, 56]. Pioglitazone has produced similarly mixed results. Treatment with pioglitazone in patients with both T2D and AD produced improvement on general cognitive status and declarative verbal memory following six months of treatment, as well as improved regional cerebral blood flow in the parietal lobe [57, 58]. Follow up data demonstrated that improvements in cognitive function were associated with reduced TNFα, supporting the anti-inflammatory actions of pioglitazone [59]. However, another trial that was designed to primarily assess the safety of pioglitazone in patients with AD failed to show any improvements on secondary outcome cognitive and functional measures [60].

The inconsistent results from clinical trials using PPAR-γ agonists have led to doubt as to whether these compounds represent effective treatments for memory disorders in older adults. In addition, safety concerns related to the effects of rosiglitazone on cardiovascular functioning and heart failure in diabetic patients have been reported. Doubts have been raised concerning reports of increased cardiovascular events with rosiglitazone [61]. Interestingly, a recent in vitro model suggested that a subclinical dose of rosiglitazone may produce more beneficial effects on Aβ clearance than higher doses [62]. Follow up animal and human studies may help to determine if lower doses may also be accompanied by a better safety/tolerability profile. Further, the above trials all included patients with clinically diagnosed AD; however, it is possible that treating insulin resistance prior to the onset of AD dementia (e.g., in early MCI or at-risk adults) may produce more favorable cognitive results.

A more recent pharmacologic approach to insulin resistance involves the use of insulinogetic glucagon-like peptide-1 (GLP-1) receptor agonists which have
Intranasal insulin

One innovative therapeutic strategy currently under investigation is the normalization of brain insulin levels through INI administration. As reviewed in the previous sections, insulin has pleiotropic effects on pathways implicated in AD pathogenesis. As such, in contrast to the majority of therapeutic approaches that focus on narrowly defined mechanisms such as acetylcholine modulation or amyloid accumulation, augmenting CNS insulin may have greater potential to comprehensively impact AD pathology. Studies administering intranasal insulin while maintaining euglycemia show increased CNS insulin and improved cognition [66–69]. However, chronic peripheral insulin administration is not a viable therapy due to risks associated with hypoglycemia and prolonged peripheral hyperinsulinemia. Any long-term treatment strategy for normalizing CNS insulin levels in persons with AD must avoid significantly increasing insulin in the periphery. There is increasing support that this may be achieved via intranasal pathways.

The nasal cavity is unique in that olfactory sensory neurons are directly exposed to the external environment in the upper nasal cavity while their axons extend through the cribriform plate to the olfactory bulb. Following intranasal administration, drugs can be directly transported to the CNS, bypassing the periphery, via extracellular pathways [70–72]. Additionally, an intraneuronal pathway delivers drugs to the CNS hours or days later [73–76]. Kern et al. [77] administered 40 IU of insulin intranasally in young, healthy adults, resulting in increased CSF insulin levels within 10 minutes of administration compared to placebo with peak levels noted within 30 minutes. CSF insulin levels had not returned to baseline by the end of the 80-minute study. Blood glucose and insulin levels did not change, demonstrating that the effects in CSF are not due to transport from the nasal cavity to systemic circulation. Although elevated CSF insulin levels do not conclusively demonstrate that brain insulin levels are similarly elevated, animal studies show labeled INI uptake to hippocampus and cortex [78]. In a murine diabetes model, INI reduced brain atrophy and neuronal NFκB activation, while increasing synaptic markers, choline acetyltransferase levels, and activation of Akt, CREB, and GSK3β. These effects were accompanied by memory enhancement on Water Maze and radial arm tasks [78].

Human functional and cognitive studies of INI also support insulin’s transport to the CNS. INI treatment induced changes in auditory-evoked brain potentials compared to placebo [77]. Several studies have reported that two months of daily insulin administration (4 × 40 IU/day) significantly improves verbal memory and enhanced mood in young healthy adults [Stockhorst et al, unpublished results, [79–82]]. In a series of studies, acute and chronic effects of INI administration on cognitive function, CSF biomarkers, and FDG-PET imaging were evaluated in memory impaired older adults. Initial pilot data from these studies showed that INI improved verbal memory acutely in persons with AD or amnestic MCI (aMCI) without affecting plasma insulin or glucose levels, and that 20 IU of insulin produced the greatest benefit [83, 84]. Subsequently, investigation of the chronic effects of 20 IU of INI [85] demonstrated that insulin treated subjects had better declarative memory and selective attention performance following 21 days of treatment. Fasting plasma insulin and glucose levels were unchanged for both groups, while Aβ42/Aβ40 ratios increased for INI-treated adults compared to placebo, reflecting increased Aβ42 relative to Aβ40.

A follow up study examined daily INI treatment for 4 months in 104 adults with AD or aMCI, and compared two doses (10 or 20 IU bid versus placebo) [86]. Compared with the placebo group, the lower dose of insulin improved delayed memory, and both insulin doses preserved caregiver-rated ability to carry out daily functions. General cognitive abilities (assessed using the Alzheimer Disease Assessment Scale), was also preserved by both doses of INI. In exploratory analyses, changes in CSF Aβ42 and tau/Aβ42 ratios were associated with cognitive and functional changes for insulin-treated participants. Participants in this trial also underwent FDG-PET imaging, compared with placebo-assigned participants, the lower dose insulin group showed reduced progression of hypometabolism in bilateral frontal, right temporal, bilateral occipital, and right precuneus/parietal regions over the 4-month treatment period. The higher dose insulin group showed even greater treatment effects indicat-
Fig. 3. Areas of hypometabolism at baseline (scan 1) and month 4 (scan 2), along with changes in hypometabolism ($\Delta$ time 2 – time 1) within each group, and differences in change between the placebo group and the 20-IU or 40-IU dose insulin group ($\Delta$ nasal insulin - $\Delta$ placebo). The red and orange colors, compared with the green and blue colors, indicate areas of greater hypometabolism from time 1 to time 2, and from placebo group to insulin groups. Reprinted from Craft et al. [86] with permission from the American Medical Association.

ing less hypometabolism progression in most regions and in left parietal cortex (Fig. 3).

The above results provide promising evidence that INI may benefit adults with aMCI or AD, and thus may represent a novel therapeutic approach to the treatment of neurodegenerative disease. Longer, larger, multi-site trials will address the question of whether INI represents a viable therapeutic approach to the treatment of AD and MCI.

LIFESTYLE MODIFICATION: STRATEGIES FOR PREVENTION

Although mediated by genetic influences, insulin resistance occurs largely as a result of lifestyle factors, including physical inactivity and hypercaloric diets high in simple carbohydrates and saturated fats. Implementation of intervention programs that address these factors could significantly reduce the social and economic burden associated with late onset dementia. Here, we examine two promising non-pharmacological strategies aimed at reducing pathological processes associated with aging and dementia: diet modification and physical exercise.

Diet modification

A typical “Western” diet consists of high levels of saturated fats and simple carbohydrates, a pattern of consumption that substantially raises the risk of insulin resistance, T2D, obesity, cardiovascular disease, and hypercholesterolemia [87–89] as well as the likelihood for cognitive impairment and AD [90–94]. Conversely, improving the dietary profile to include reduced saturated fat and increased mono and polyunsaturated fats may produce protective effects on cognitive function-
and vegetables, and is low in saturated fats and simple carbohydrates, has received a great deal of attention for its association with reduced risk for both AD and MCI [100–102].

We recently conducted a controlled intervention aimed at examining the effects of diet on cognitive function and CSF biomarkers in older adults with and without cognitive impairment [29]. Participants consumed a high-saturated fat, high glycemic index (HIGH) diet (a pattern associated with T2D and insulin resistance), or a low-saturated fat, low glycemic index (LOW) diet for four weeks. CSF AD and inflammatory markers were measured before and after diet. The diet interventions successfully modulated insulin and lipid metabolism without changing body weight, allowing us to examine the effects of diet-induced metabolic changes on AD biomarkers. For normal adults, the HIGH diet moved CSF biomarkers in a direction that may characterize a pre-symptomatic adult, the HIGH diet moved CSF biomarkers in a direction that may characterize a pre-symptomatic metabolic changes on AD biomarkers. For normal adults, the HIGH diet moved CSF biomarkers in a direction that may characterize a pre-symptomatic AD prior to plaque deposition, increasing total Aβ42 and F2-IsoProstanes, and lowering insulin. AD biomarkers were unaffected by the HIGH diet for adults with aMCI possibly because more extreme intervention is needed to exacerbate pathological processes already extant. However, both aMCI and normal groups showed beneficial effects of the LOW diet, including improved CSF Aβ42 profiles, reduced F2-IsoProstanes and ApoE, and improved memory. Our results support further investigation into the possibility that consumption of a diet high in saturated fat and simple carbohydrates that induces peripheral insulin resistance may contribute to pathological processes in the brain that increase the risk of AD, and that a healthy diet may protect against these processes. Taking together, these animal, population-based and human intervention studies suggest that dietary factors may influence the expression of AD.

Physical exercise

A sedentary lifestyle is likely a key factor in the increase in insulin resistance-related conditions noted in recent years. Aerobic exercise, known to be an effective treatment for diabetes and related conditions, also has potent salutary effects in the brain [103, 104]. Increased physical activity is consistently linked with improved learning and memory both in humans and in animal models [105]. The favorable effects of exercise are likely exerted through multiple pathways known to be influenced by insulin resistance, including improved cardiovascular and cerebrovascular function [106, 107], anti-inflammatory processes [108, 109], and enhanced insulin-dependent energy metabolism [110]. Thus, aerobic exercise has the potential to modify multiple processes compromised in pathological brain aging.

Observational studies suggest that moderate physical activity throughout the lifespan is associated with improved cognitive function and reduced dementia risk in older age. Regular exercise during mid-life, when many pathological disease processes likely begin, has been linked to reduced dementia risk and improved cognitive profile in older adults [111, 112]. Long-term exercise has been shown to impact AD pathology as well. In a recent study, older adults who exercised at least thirty minutes per day, five days per week for at least ten years demonstrated lower brain Aβ deposition (using Pittsburgh compound B on PET scan) [113]. Recently, physical exercise has received attention as a potentially effective non-pharmacological strategy to prevent or slow decline in older adults already experiencing mild cognitive changes [114]. Although there are a limited number of intervention trials that specifically target MCI, initial results from studies that include moderate- to high-intensity exercise interventions present promising results. In a small randomized controlled 6-month trial of aerobic exercise versus a stretching control condition for sedentary adults with MCI [115], we found that the aerobic exercise condition improved cardiorespiratory fitness, increased insulin sensitivity, reduced plasma Aβ levels, and augmented performance on multiple executive function tasks. Similarly, in a 6-month randomized controlled trial [116], subjects who exercised at a moderate intensity level demonstrated significant improvements on the Alzheimer Disease Assessment Scale. Future studies will focus on the specific “dose” and type of exercise needed for beneficial effects to occur, and the mechanisms through which exercise mitigates AD pathological processes.

CONCLUSIONS

The recognition of AD as a heterogeneous disorder that results from incremental pathological changes in dynamic organismic systems is essential to move beyond the unidimensional approaches to prevention and therapy that have proven largely ineffective to date. Biological systems related to insulin metabolism are arguably the most critical regulators of longevity and corporeal aging. Our work has focused on identifying the relationship of the insulin network to brain aging, and determining the mechanisms through which...
insulin dysregulation promotes AD pathological processes. It is likely that different nodes of the insulin network are perturbed for subgroups of AD patients, or that for some subgroups, pathways independent of insulin are critical pathogenetic factors. New methods from systems network analyses may help to identify these subgroups, which will be critical for devising tailored prevention and treatment strategies. From a public health perspective, the simultaneous increase in the aging population and in the prevalence of insulin resistance raises the specter of a rapid escalation in the incidence of dementia. Fortunately, insulin resistance and related factors can be identified prior to the onset of AD, at a stage where lifestyle modification or therapeutic intervention may have the greatest likelihood of success.

DISCLOSURE STATEMENT


REFERENCES


[26] Xu QL, Yang F, Rosato ER, Ubeda OJ, Beech W, Gant DL, Chen PP, Bluudith B, Chen C, Zhao Y, Vin-
sensory, via the hypothalamic region, which is the site of the pathogenesis of Alzheimer’s disease, *Behav Brain Res* **78**, 37-41.


Memory improvement following induced hyperinsulinaemia in Alzheimer’s disease. Neuroendocrinology 17, 123-130.


