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Insulin resistance syndrome and Alzheimer's disease: Age- and obesity-related effects on memory, amyloid, and inflammation

Suzanne Craft *

Geriatric Research, Education, and Clinical Center, Veterans Affairs Puget Sound Health Care System, Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, GRECC S-182, VAPSHCS, 1660 S. Columbian Way, Seattle, WA 98108, USA

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Abstract

Insulin plays an important role in memory and other aspects of brain function. The insulin resistance syndrome, characterized by chronic peripheral insulin elevations, reduced insulin activity, and reduced brain insulin levels, is associated with age-related memory impairment and Alzheimer's disease (AD). Our work has focused on specific mechanisms through which this association is forged, including the effects of peripheral hyperinsulinemia on memory, inflammation, and regulation of the β-amyloid peptide that plays a key role in AD pathophysiology. Our data suggest that excessive insulin invokes synchronous increases in levels of Aβ and inflammatory agents, effects that are exacerbated by age and obesity. This constellation of events may have deleterious effects on memory. Treatments focused on preventing or correcting insulin abnormalities may be of therapeutic benefit for adults with age-related memory impairment and AD.

Keywords: Insulin; Alzheimer; Amyloid; Diabetes; Inflammation; Obesity

1. Introduction

In recent years, our work has focused on understanding the role of insulin in cognition, and the manner in which abnormalities of insulin metabolism contribute to disorders of aging, and in particular to the pathogenesis of Alzheimer's disease (AD). This knowledge has become increasingly important given the pandemic of conditions related to insulin dyregulation, such as obesity, diabetes, cardiovascular disease, and hypertension.

In a number of studies, we and others have demonstrated that insulin facilitates memory when administered at optimal doses and in the context of sufficient basal glucose availability. This facilitation has been observed with direct intracerebroventricular administration of insulin in rodents [15], as well as with intravenous insulin administration in humans [3], which induces the transport of insulin into the CNS across the blood brain barrier (BBB). More recently we have demonstrated the facilitation of memory in patients with AD with intranasal insulin administration [16], a procedure which allows insulin-like peptides direct access to the brain without affecting peripheral glucose or insulin levels. A number of mechanisms may plausibly contribute to insulin-mediated memory facilitation. As we have previously reviewed, insulin receptors are present in key brain regions, such as hippocampus, entorhinal cortex, and frontal cortex [5]. Insulin has been shown to modulate glucose utilization in CNS (although it does not appear to affect basal brain glucose uptake) [2]. It also modulates levels of classic neurotransmitters such as acetylcholine, norepinephrine, and dopamine that play important roles in cognition. Insulin also affects membrane potentials, neuronal physiology, and long-term potentiation, all of which influence the synaptic remodeling processes thought to underlie memory formation [5].

* Tel.: +1 206 277 1156; fax: +1 206 764 2569.
E-mail address: scraft@u.washington.edu.

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Problems arise when the normal actions of insulin are subverted. The most common condition creating such subversion is the insulin resistance syndrome, characterized by persistent high levels of insulin in the periphery, and a reduced ability of insulin to carry out various functions, such as mediating glucose uptake into muscle. Insulin resistance syndrome is exceedingly common in older adults; current estimates indicate that approximately half of all adults over 60 years of age are affected. One lesser-known consequence of insulin resistance and chronic peripheral hyperinsulinemia is the down-regulation of insulin transport into brain, which ultimately leads to a brain insulin deficient state [1]. As a result, the brain is deprived of the many beneficial influences of insulin. Concomitantly, in the periphery, chronic hyperinsulinemia induces elevations in free fatty acids and inflammatory cytokines, an effect that is exacerbated by obesity [7].

We have modeled the effects of hyperinsulinemia acutely in older adults and in patients with AD using a hyperinsulinemic-euglycemic clamp. With this technique, insulin is infused intravenously at a continuous rate designed to reach a pre-determined level, while dextrose is administered as needed at a variable rate to maintain euglycemia. With low doses of insulin, memory is facilitated for normal older adults. A subgroup of patients with AD who are most likely to have insulin resistance syndrome require higher insulin doses to show memory facilitation [3]. At higher than optimal doses, memory facilitation is attenuated. Excessive hyperinsulinemia also induces a number of undesirable physiologic effects. One such effect is modulation of peptides that are known to play an important role in the pathology of AD. The β-amyloid peptide (Aβ) aggregates in the senile plaques that constitute a hallmark of AD pathology. Aβ is characterized by a tendency to form oligomeric assemblies that may directly and negatively affect memory function. For example, raising β-amyloid to levels that do not affect the viability of cortical neurons suppresses phosphorylation of the cyclic adenosine monophosphate response element binding protein (CREB) and interferes with downstream events such as the activation of brain-derived neurotrophic factor (BDNF) [17]. Assemblies also disrupt memory acutely, possibly through effects on long-term potentiation [18,21]. We have shown that acute hyperinsulinemia induced through insulin infusion increases levels of the Aβ peptide in cerebrospinal fluid (CSF) in an age-dependent manner (Fig. 1A), compared with a control condition in which saline was infused [20]. Further, greater increases in Aβ in response to hyperinsulinemia were accompanied by an attenuation of insulin's ability to facilitate memory (Fig. 1B). These findings suggest that for many older adults peripheral hyperinsulinemia accompanying the insulin resistance syndrome may induce Aβ elevations, which in turn contribute to age-related memory impairment and the development of AD.

We have also examined the effects of peripheral hyperinsulinemia on inflammation in the central nervous system. In the periphery, insulin modulates many aspects of the inflammatory network, with anti-inflammatory actions observed at low doses and pro-inflammatory effects at high levels [6]. Using our acute infusion paradigm, we determined that hyperinsulinemia produced robust increases in CSF levels of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α), as well as in levels of a brain-derived marker of lipid peroxidation, F2-lsoProstane [8]. Effects were greatest for participants with the highest body mass index for CSF TNFα, a cytokine that inhibits Aβ transport from brain to periphery. These data represented the first demonstration that excessive peripheral insulin elevation increases inflammation in the central nervous system. Furthermore, the degree of increase from F2-lsoProstane, an eicosonoid produced only by neurons and glia, was positively correlated with changes in Aβ levels. Our results suggest that synchronous hyperinsulinemia-induced increases in Aβ and inflammation may represent an important pathway through which the insulin resistance syndrome increases the risk for AD.

2. A model of peripheral hyperinsulinemia, insulin resistance, and AD pathogenesis

In the preceding sections, we have reviewed evidence supporting the notion that high plasma insulin levels and peripheral insulin resistance can affect cognition, Aβ42, and inflammation in the CNS. From such evidence, a model can be constructed describing how this metabolic profile contributes to the pathogenesis of AD. There are likely several etiologies

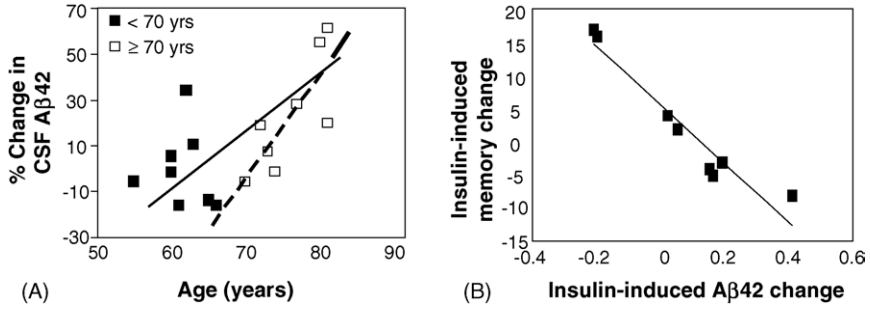

Fig. 1. (A) Percent CSF Aβ42 increase following insulin infusion relative to saline infusion was age-dependent, with older adults showing larger increases ($p < .01$). (B) Insulin-induced Aβ42 changes were negatively correlated with insulin-induced memory facilitation for older (age > 70 years) adults ($r = -.95$, $p < .01$). Taken from Watson et al. [20].

leading to the final common expression of AD pathology. The model we are proposing is one potential etiology, and as such does not necessarily apply to all AD patients. It is, however, a model with relevance to a rapidly growing segment of our population. The root conditions in this model, peripheral hyperinsulinemia and insulin resistance, are mutually reinforcing (each can cause or exacerbate the other), and may result from a number of causes, including genetic vulnerability and/or environmental factors, such as diet and inactivity. They are also increasingly common conditions, in part due to the complexity of insulin signaling pathways, and in part due to pervasive changes in diet and physical activity occurring at an unprecedented rate in Western societies.

The first component of our model concerns the effects of chronic peripheral hyperinsulinemia and insulin resistance on brain insulin levels. Peripheral hyperinsulinemia and insulin resistance down-regulate brain insulin uptake at the BBB, resulting in long-term reduction of brain insulin levels. This phenomenon has been modeled in vivo in dogs with diet and glucocorticoid-induced insulin resistance [1,13] and was also observed in diet-induced insulin resistant Tg 2576 mice, a rodent model of AD (G. Pasinetti, personal communication). Furthermore, we have shown that patients with AD have lower CSF insulin levels, higher plasma insulin levels, and reduced CSF to plasma insulin ratios compared to healthy controls [4]. Insulin promotes the release of intracellular Aβ [9], and regulates expression of insulin-degrading enzyme, a protease critical for the efficient clearance of Aβ [22]; thus, abnormally low brain insulin levels may result in increased intraneuronal accumulation of Aβ and reduced levels of a protease that plays a major role in its clearance. Lowered brain insulin also has effects that may not be directly related to Aβ regulation, such as decreased neurotransmitter and energy availability, and impedance of LTP. As a consequence of these effects, insulin's normal facilitation of memory processes and Aβ regulation would be abrogated, leading to the memory impairment and Aβ accumulation that are hallmarks of the disease.

A second component of our model relates to the effects of peripheral hyperinsulinemia in AD which may inhibit the clearance of Aβ42 from the brain into the periphery. The obstruction of this peripheral "sink" can presumably occur either by blocking Aβ transport from brain, or by interfering with Aβ clearance in peripheral sites, and as a result may promote excessive brain Aβ42 accumulation. There may be several sites of peripheral Aβ clearance. For example, the liver has been proposed as one of the primary clearance sites [10]. Hepatic insulin resistance such as has been associated with prolonged hyperinsulinemia and glucocorticoid elevations may thus interfere with this process. Conversely, chronic or extreme insulin elevations may inhibit peripheral Aβ clearance, in part because high insulin levels compete for the attention of IDE, the protease believed to play a major role in Aβ degradation, that is highly expressed in peripheral sites such as liver, kidney, and muscle. Insulin resistance also inhibits IDE activity, further contributing to decreased Aβ clearance. Thus, the combined effects of insulin resistance and hyperinsulinemia in liver and other peripheral sites may reduce Aβ uptake and degradation, leading to the high levels of plasma Aβ42 documented in some AD patients [14]. Recent findings suggest that plasma Aβ levels are elevated in prodromal and early disease stages. Obstruction of Aβ clearance through peripheral channels may ultimately result in excess accumulation in brain.

A third component of the model concerns the effects of peripheral hyperinsulinemia and insulin resistance on inflammation in the brain and CNS vascular endothelium. Our data indicate that hyperinsulinemia's effects on inflammation in the CNS are pervasive, provoking striking increases in CSF levels of TNFα, IL-1β, IL-6 and the lipid peroxidation marker F2-lsoprostane. In a recent study, hyperinsulinemia-induced elevations in CSF Aβ42 were directly correlated with CSF IL-6 and F2-lsoprostane levels. Thus, peripheral hyperinsulinemia and insulin resistance may instigate a mutually reinforcing "Aβ-inflammation cycle" as proposed by Griffin et al. [11]. The effects of insulin on inflammation are likely to be potentiated by obesity, given that insulin induces elevations in TNFα and FFA release from adipocytes.

To summarize our model as shown in Fig. 2, peripheral insulin resistance and hyperinsulinemia increase peripheral FFA levels, with concomitant increases in inflammatory agents such as TNFα in the periphery and CNS. Peripheral hyperinsulinemia and insulin resistance reduce Aβ uptake and clearance in liver and other peripheral sites, causing a rise in peripheral Aβ levels. Effects on FFAs, TNFα, and plasma Aβ are exacerbated by increased adiposity. Plasma Aβ elevations interfere with clearance from brain to periphery, or enhance Aβ transport into brain. Peripheral insulin resistance and hyperinsulinemia also lead to a depletion of brain insulin levels. As a result, intraneuronal Aβ release is inhibited and IDE levels are lowered, further promoting intraneuronal Aβ accumulation. The accumulation is compounded by obstruction of clearance through the periphery and by increased inflammation in brain. The resulting effects induce the hallmark memory impairment and pathophysiological characteristics of AD.

3. Implications for therapy

Our model suggests that lowering of peripheral insulin levels and enhancing insulin sensitivity may improve cognitive function in aging. Lifestyle interventions such as exercise have potent insulin-sensitizing effects and may provide real benefit in this regard. We are currently examining the potential benefit of exercise on memory for adults with amnestic mild cognitive impairment, widely believed to be a prodromal phase of AD. Alternatively, pharmacologic treatment with insulin-sensitizing compounds such as the thiazolidinediones (TZD) may offer some therapeutic relief. We have recently demonstrated that 6 months of treatment with rosiglitazone, a TZD used for Type 2

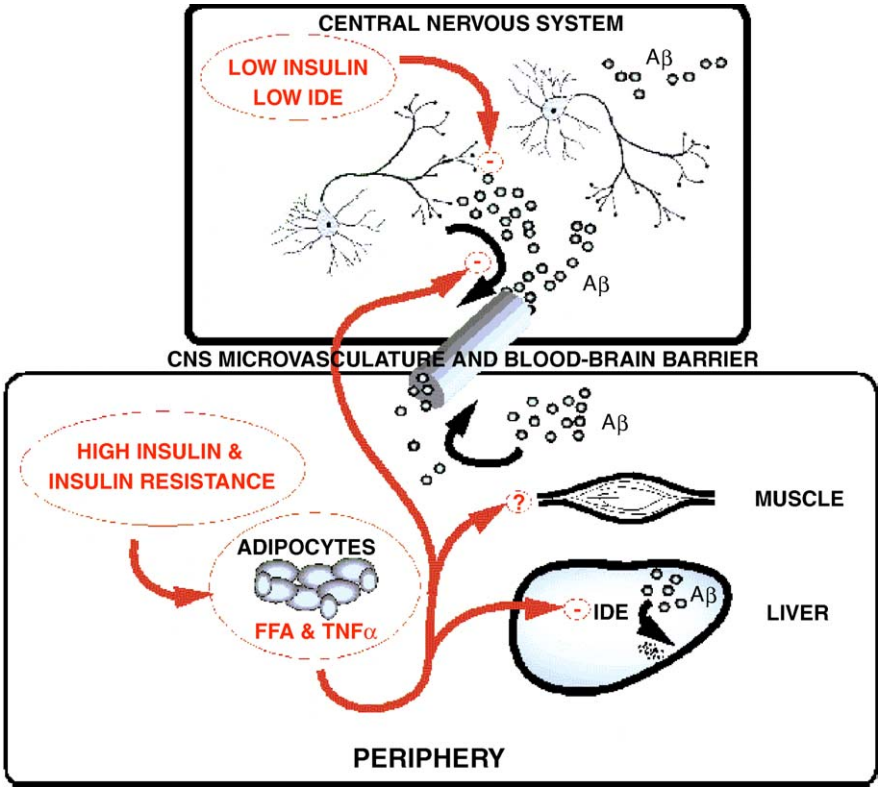

Fig. 2. Model of the effects of peripheral insulin resistance and hyperinsulinemia on central nervous system insulin, IDE, and Aβ levels.

diabetes mellitus, preserved memory function for patients with AD compared to a placebo-assigned group [19]. Finally, correcting the brain insulin deficiency which putatively accompanies peripheral insulin resistance may also have some therapeutic benefit. We recently determined that intranasal administration of insulin, a procedure that raises insulin in the CNS without affecting peripheral levels, enhanced memory for a subgroup of patients with AD [16].

4. Summary

Insulin plays an important role in memory and other aspects of brain function. Peripheral hyperinsulinemia and insulin resistance induce a number of deleterious effects in the central nervous system that interfere with these functions, in a manner that is exacerbated by obesity and aging. In particular, effects on Aβ regulation and inflammation are potential culprits in promoting aging-related memory impairment and AD. This possibility has obvious relevance for adults with T2DM; however, it is worth noting that hyperinsulinemia and insulin resistance afflict many non-diabetic adults with conditions such as obesity, impaired glucose tolerance, cardiovascular disease, and hypertension. Our work provides a foreboding note for the current plethora of conditions associated with insulin resistance and hyperinsulinemia. In the context of an aging population, these conditions may provoke a dramatic increase in the prevalence of AD. More encouragingly, identification of the mechanisms through which insulin resistance and hyperinsulinemia promote AD pathogenesis may lead to novel and more effective strategies for treating, delaying, or even preventing this tragic disease.

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