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Insulin, cognition, and dementia

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Abstract

Cognitive disorders of aging represent a serious threat to the social and economic welfare of current society. It is now widely recognized that pathology related to such conditions, particularly Alzheimer's disease, likely begins years or decades prior to the onset of clinical dementia symptoms. This revelation has led researchers to consider candidate mechanisms precipitating the cascade of neuropathological events that eventually lead to clinical Alzheimer's disease. Insulin, a hormone with potent effects in the brain, has recently received a great deal of attention for its potential beneficial and protective role in cognitive function. Insulin resistance, which refers to the reduced sensitivity of target tissues to the favorable effects of insulin, is related to multiple chronic conditions known to impact cognition and increase dementia risk. With insulin resistance-associated conditions reaching epidemic proportions, the prevalence of Alzheimer's disease and other cognitive disorders will continue to rise exponentially. Fortunately, these chronic insulin-related conditions are amenable to pharmacological intervention. As a result, novel therapeutic strategies that focus on increasing insulin sensitivity in the brain may be an important target for protecting or treating cognitive decline. The following review will highlight our current understanding of the role of insulin in brain, potential mechanisms underlying the link between insulin resistance and dementia, and current experimental therapeutic strategies aimed at improving cognitive function via modifying the brain's insulin sensitivity.

Keywords

Alzheimer's disease; insulin; cognition; diabetes; aging

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1. Introduction

Insulin, long considered to be a hormone that primarily exerts its influence in the periphery, is now known to have potent effects in the brain. Insulin resistance refers to the reduced ability of insulin to exert its action on target tissues and is associated with neuropathological processes that underlie cognitive aging and dementia. Several risk factors implicated in cognitive decline, including diabetes, hyperlipidemia, hypertension, and obesity, are closely linked to underlying insulin dysfunction. Given the rise in such chronic conditions, in combination with a rapidly aging population, the prevalence of Alzheimer's disease and other cognitive disorders is likely to continue to rise exponentially. Recent clinical trials have focused on identification of novel potential therapeutic mechanisms aimed at improving insulin sensitivity in the brain; with the expectation that these mechanisms may represent promising treatments for cognitive disorders of aging. This review will focus on the effects of insulin in the central nervous system, the relationship between insulin-associated conditions and dementia, and potential mechanisms for the pharmacological treatment of insulin resistance in brain.

2. The role of insulin in the brain

Insulin, a peptide secreted by pancreatic beta cells, is readily transported into the central nervous system across the blood brain barrier by a saturable, receptor-mediated process (Banks et al., 1997a; Baskin et al., 1987; Baura et al., 1993). Insulin receptors are abundant in the synapses of both astrocytes and neurons, and are selectively distributed in the olfactory bulb, cerebral cortex, hippocampus, hypothalamus, amygdala, and septum (Baskin et al., 1987; Havrankova et al., 1978a; Havrankova et al., 1978b; Unger et al., 1991). Here, insulin signaling contributes to both synaptogenesis and synaptic remodeling (Abbott et al., 1999).

Beyond direct effects at the receptor site, insulin exerts additional neuromodulatory actions that have implications for cognition. For example, insulin may augment the induction of long-term potentiation, thought to be the primary cellular basis for memory formation, by influencing cell membrane expression of *N*-methyl-D-aspartate receptors (Skeberdis et al., 2001). Insulin also regulates expression of the neurotransmitters acetylcholine and norepinephrine, both of which are known to influence cognition (Figlewicz et al., 1993; Kopf and Baratti, 1999). Further, insulin may act to increase cortical cerebral glucose metabolism in brain regions important for learning and memory (Bingham et al., 2002). Regional insulin effects on glucose metabolism may be related to the distribution of insulin-sensitive glucose transporter isoforms 4 and 8 (Reagan et al., 2001; Schulingkamp et al., 2000), which in the rat brain are selectively distributed in the cerebellum, sensorimotor cortex, hippocampus, pituitary, and hypothalamus (glucose transporter isoform 4) and in the hippocampus and hypothalamus (glucose transporter isoform 8) (Reagan et al., 2001). Insulin has been shown to increase brain glucose transporter isoform 4 expression and translocation (Piroli et al., 2007), and substantial co-localization exists for insulin-containing neurons, insulin receptors and both glucose transporter isoforms 4 and 8 (Apelt et al., 1999; Schulingkamp et al., 2000).

Given numerous influences of insulin in selective brain regions, including medial temporal lobe structures that support learning and memory, it is not surprising that there is a growing literature that links insulin to cognitive function. In both rat models and human studies, acute insulin administration reliably improves memory (Unger et al., 1991) (Craft et al., 2003; Craft et al., 1999; Craft et al., 1996; Kern et al., 2001). Interestingly, the learning process itself is also accompanied by changes in insulin signaling molecules in the hippocampus. This was demonstrated by increased insulin receptor expression in the dentate gyrus and hippocampal CA1 field in rodents trained on a spatial memory task (Zhao et al., 1999). Together, these studies support that insulin may play an important role in regulating normal cognitive function.

3. Insulin resistance and Alzheimer's disease pathology

While acute hyperinsulinemia may produce beneficial effects on cognition, persistently high levels of circulating insulin may conversely exert a negative influence on memory and other cognitive functions. Raising peripheral insulin levels acutely elevates brain and cerebrospinal fluid insulin levels, whereas prolonged peripheral hyperinsulinemia down-regulates insulin receptors at the blood-brain barrier and reduces insulin transport into the brain (Schwartz et al., 1990; Wallum et al., 1987). Chronically elevated insulin can thus lead to insulin resistance, characterized by high peripheral insulin and diminished insulin-mediated glucose clearance (Reaven, 1983, 2003). Such high levels of insulin over time can render tissue unresponsive to insulin, resulting in substantial damage to muscle, liver, adipose tissue, endothelium, and brain. The insulin resistance syndrome has been linked to several chronic medical conditions, including cardiovascular disease, metabolic syndrome, diabetes, and increasingly, dementia. However, the pancreas is able to compensate by generating adequate levels of insulin to maintain lower glucose levels for some time prior to the onset of frank disease. Thus, abnormally high levels of peripheral insulin may be silently contributing to the initiation of the Alzheimer's disease pathology cascade in some individuals years or decades prior to initial clinical dementia symptoms (Xu et al., 2009).

3.1. Evidence for insulin resistance in the Alzheimer brain

Hoyer and colleagues were the first to suggest that desensitization of the neuronal insulin receptor plays a role in Alzheimer's disease by demonstrating a reduction in insulin receptors and tyrosine kinase activity markers in the Alzheimer brain. (Frolich et al., 1998; Hoyer, 2002) Subsequently, reduced insulin and insulin-like growth factor 1 message was shown to correlate with increasing Alzheimer pathology and cholinergic deficit (Rivera et al., 2005). Recently, through a series of *ex vivo* experiments in autopsied cognitively normal participants and patients with Alzheimer's disease, brain insulin resistance was demonstrated (particularly in the hippocampus) and was associated with clinical symptoms of cognitive decline prior to death (Talbot et al., 2012). Such insulin resistance was determined to be independent of type 2 diabetes diagnosis or apolipoprotein E genotype. Collectively, these findings provide support that Alzheimer's disease is associated with insulin resistance in the brain.

3.2. Insulin regulation of beta amyloid

Increasingly, *in vitro* and animal studies show that insulin has robust effects at multiple points during the amyloid cascade, and thus in all likelihood can modulate the process by which the beta amyloid (A β) peptide aggregates in the brain. In both rat and human cell cultures, insulin reduces the phosphorylation of amyloid precursor protein and increases proteins that are anti-amyloidogenic in nature, including insulin degrading enzyme, β -secretase, and glycogen synthase kinase-3 β (Pandini et al., 2013). Further, insulin fosters the release of intracellular A β in neuronal cultures, affecting both its short (A β 40) and long (A β 42) forms and accelerating their trafficking from the Golgi and trans-Golgi network to the plasma membrane (Gasparini et al., 2001; Pandini et al., 2013). Thus, in the presence of reduced brain insulin, the trafficking of A β from intracellular to extracellular compartments may be compromised.

Increasingly, the role of impaired A β clearance, rather than increased production of A β , has been recognized as a key factor in the development of late-onset Alzheimer's neuropathology. Insulin degrading enzyme, a metalloprotease that catabolizes insulin, is highly expressed in brain (Authier et al., 1996) and is recognized as having an essential role in both A β clearance (Kurochkin and Goto, 1994; McDermott and Gibson, 1997; Qiu et al., 1998; Zhao et al., 2004) and intracellular degradation (Sudoh et al., 2002). Postmortem brain tissue from Alzheimer's patients shows lower overall levels of insulin degrading enzyme and messenger ribonucleic acid, as well as reduced insulin degrading enzyme activity. In addition, insulin degrading enzyme knockout mice have reduced insulin in brain as well as muted degradation of A β and insulin in brain (Cook et al., 2003; Farris et al., 2003; Perez et al., 2000). Thus, through reducing levels of insulin degrading enzyme in brain, low levels of insulin in the central nervous system may interfere with A β clearance.

Chronic peripheral hyperinsulinemia has been associated with a pattern in which brain insulin levels are initially higher, then decrease as transport of insulin into the brain is down-regulated (Banks et al., 1997b). Consistent with this pattern, it has been shown that genetically obese Zucker rats have reduced insulin binding to brain capillaries (Schwartz et al., 1990) and reduced hypothalamic insulin levels (Gerozissis et al., 1993) in comparison with lean controls. Additionally, brain uptake of labeled insulin was reduced and peripheral insulin clearance was inhibited in insulin resistant canines (Kaiyala et al., 2000). Adults with Alzheimer's disease show lower insulin levels in cerebrospinal fluid, higher plasma insulin levels, and reduced cerebrospinal fluid to plasma insulin ratios compared to healthy controls (Craft et al., 1998). High plasma insulin levels may interfere with degradation of A β transported out of the brain, thereby obstructing a peripheral A β -clearing "sink." Concomitantly, low brain insulin levels reduce release of A β from intracellular compartments into extracellular compartments where clearance is believed to occur. Thus, for some patients with Alzheimer's disease, high peripheral insulin levels and low brain insulin levels would result in reduced clearance of A β both in brain and in the periphery.

Support for the validity of this model is provided by a recent study that induced insulin resistance in the transgenic 2576 (Tg2576) mouse model of Alzheimer's disease with a high fat diet. Diet manipulation resulted in a metabolic profile of high peripheral insulin, and low brain insulin and insulin degrading enzyme levels compared with Tg2576 mice fed a normal

diet (Ho et al., 2004). Diet-induced insulin resistance caused two-fold increases in A β 40 and 42, and earlier, larger A β deposits compared with non-insulin resistant Tg2576 mice. Furthermore, insulin resistant mice had impaired learning on a water maze test. These results are consistent with a subsequent study showing that insulin regulates insulin degrading enzyme and A β through a phosphatidylinositol-3-kinase-dependent signaling mechanism (Zhao et al., 2004), in which treatment of primary hippocampal neurons with insulin produced a 25 percent increase in insulin degrading enzyme expression. In another model of insulin resistance, amyloid precursor protein/presenilin-1 transgenic mice were given sucrose sweetened beverages, and also demonstrated increased brain A β deposition and reduce Morris water maze learning (Cao et al., 2007). Together these results suggest that insulin resistance can precipitate the neuropathological and behavioral features of Alzheimer's disease, and that raising brain insulin levels may reduce neuropathological changes related to the disease.

3.3. A β regulation of brain insulin signaling

Conversely, A β also regulates insulin signaling in the brain. Soluble A β binds to the insulin receptor and disrupts its signaling capacity and induction of long-term potentiation in mouse hippocampal slice preparations (Townsend et al., 2007). These effects were prevented by pre-treatment of the tissue with insulin prior to A β exposure. Synthetic soluble A β oligomers, known as A β -derived diffusible ligands, downregulate plasma membrane insulin receptors in primary hippocampal cultured neurons, leading to synaptic spine loss. This process was also prevented by pre-treatment with insulin (De Felice et al., 2009). A related mechanism through which insulin and A β may interact to modulate Alzheimer's pathology is via synaptotoxic effects. Loss of synapses is the earliest structural defect observed in Alzheimer's disease. Soluble oligomeric species of A β are synaptotoxic, and insulin prevents binding of A β to synapses, thereby preserving synaptic integrity (De Felice et al., 2009). Insulin also reduces oligomer formation which may have additional protective effects; a functional consequence of these effects appears to be protection against A β -induced disruption of long term potentiation integrity, the process of synaptic remodeling believed to underlie memory formation (Lee et al., 2009). Collectively, these findings suggest that soluble A β may induce neuronal insulin resistance and synapse loss.

3.4. Other Alzheimer's-related mechanisms

In addition to insulin's role in A β clearance and degradation, insulin also inhibits phosphorylation of tau, the protein that forms neurofibrillary tangles, a neuropathological hallmark of Alzheimer's disease and other dementing processes. Insulin may affect tau through its regulation of glycogen synthase kinase 3 β , a downstream target in the insulin signaling pathway (Hong and Lee, 1997). Schubert and colleagues (Schubert et al., 2004) abolished insulin signaling *in vivo* with a conditional knockout mouse model in which the insulin receptor gene was inactivated in the central nervous system. Phosphorylation of glycogen synthase kinase 3 β and Akt was reduced and phosphorylation of tau increased 3.5-fold. Recent work also implicates insulin receptor substrate 2, in that mice in which this gene has been knocked out have increased tangles and hyperphosphorylated tau (Schubert et al., 2003). Further, insulin dysregulation is also associated with oxidative stress,

inflammation, and impaired neurogenesis (Craft and Watson, 2004). Figure 1 demonstrates the potential consequences of insulin resistance on Alzheimer pathology in the brain.

4. Insulin resistance-related conditions and dementia

Above, we provide compelling evidence that insulin resistance alone is a viable candidate risk factor for Alzheimer's disease. Indeed, recent studies have associated insulin resistance with Alzheimer-consistent impairments on functional imaging scans. For example, insulin resistance (defined as having high levels of fasting plasma insulin) in middle-aged women was associated with reduced activity in the prefrontal cortex and hippocampal regions, which corresponded with reductions in performance on neuropsychological test performance (Kenna et al., 2013). Reductions in cerebral glucose metabolism in prefrontal, temporal, and cingulate regions identified by fludeoxyglucose F 18-positron emission tomography were noted in prediabetic and diabetic older adults as compared to nondiabetic adults (Baker et al., 2011) (Figure 2). Despite these small experimental studies, because insulin resistance is often not identified in its earliest stages in the absence of its related chronic conditions, it is often not studied in population-based models. Thus, in the following sections, we focus on the increased dementia risk associated with insulin resistance-related syndromes.

4.1. Diabetes

The repeated connection between insulin and mechanisms related to Alzheimer's disease pathology have led some to refer to Alzheimer's disease as "Type 3 diabetes" (de la Monte and Wands, 2008). Indeed, Type 2 diabetes predicts cognitive decline in older adults (Tilvis et al., 2004) and confers a significantly increased risk of both Alzheimer's disease and vascular dementia (Luchsinger, 2008; Strachan et al., 2008). A recent meta-analysis found that 14 of 15 community-based studies reported positive associations between diabetes and Alzheimer's disease, with a pooled population-attributable risk of 8% (Tolppanen et al., 2013). In the prospective, community-based Rotterdam study, Ott et al. (Ott et al., 1996) found that Type 2 diabetes significantly increased the risk for all-cause dementia and Alzheimer's disease, with greater risk apparent in people who were insulin-treated (and therefore likely to be in the more severe stages of the disease) at baseline. Similar results were reported by Leibson et al (Leibson et al., 1997) and the Religious Orders Study reported a 65% increased risk for Alzheimer's disease among those with Type 2 diabetes (Arvanitakis et al., 2004). Findings from the Mayo Clinic Alzheimer's Disease Patient Registry show an increased prevalence of diabetes (35% vs. 18% in non-demented control subjects) and impaired glucose tolerance (46% vs. 24%) for patients with Alzheimer's disease (Janson et al., 2004). Further, Alzheimer's risk is raised independently from vascular or other dementias (Maher and Schubert, 2009; Ott et al., 1999), a finding that is not surprising given the wealth of literature that connects insulin dysfunction with Alzheimer-specific brain pathology.

Despite the associations between cognitive decline and type 2 diabetes, recent neuropathological studies have produced somewhat conflicting results. One study showed that dementia patients with treated diabetes had A β plaque loads that were similar to those of non-demented controls, while untreated diabetic dementia patients had plaque loads

consistent with dementia patients without diabetes (Beeri et al., 2008). Treated diabetics with dementia had higher levels of microvascular infarcts and antiinflammatory markers to a degree not present in untreated diabetics (Sonnen et al., 2009). Given the preliminary nature of these results and small sample sizes, these studies must be replicated prior to making any firm conclusions as to their meaning. If supported by larger studies, however, these findings could bring into question the relative impact of both A β and microvascular disease in the development of clinical dementia symptoms. It is possible that treated diabetics, who are likely to be at a more advanced stage of disease, express the symptoms of dementia at lower levels of amyloid burden due to co-existing microvascular damage. Future neuropathological studies that carefully examine disease duration, treatment duration and dose, and concomitant vascular risk factors will certainly help to clarify these questions.

4.2 Dyslipidemia

Insulin resistance is associated with dyslipidemia, and lipid metabolism may be related to A β accumulation. Animal models show greater very low density lipid secretion in advance of A β deposits in the brain (Burgess et al., 2006), and Alzheimer's disease is associated with increased post-prandial chylomicron and low density lipid levels (Mamo et al., 2008). By increasing lipolysis and free fatty acids in adipocytes, insulin resistance leads to an influx of free fatty acids into the liver. This inhibits insulin-mediated suppression of very low density lipid secretion, which is crucial for preventing post-prandial hyperlipidemia and for maintaining an optimal lipid balance (Kamagate et al., 2008). Insulin resistance thus results in higher and more prolonged post-prandial very low density and other lipids, a process that may represent yet another pathway by which insulin potentially exacerbates pathological A β processes in the brain. Despite these findings, the connection between cholesterol and dementia is complex. High plasma cholesterol at midlife is associated with higher A β 40 levels (Smith and Betteridge, 2004) and a 2–3 fold increased risk for later Alzheimer's disease dementia (Anstey et al., 2008). Late-life total cholesterol, however, does not appear to be associated with an increased Alzheimer's disease risk (Anstey et al., 2008), and may in fact be protective to some degree (Cedazo-Minguez et al., 2011; Reitz et al., 2005).

4.3 Vascular impairment and hypertension

Insulin dysfunction can substantially impact the vasculature via direct effects, hyperlipidemia, and inflammation. Insulin plays a modulatory role in capillary recruitment, vasodilation, and regional blood flow (Cersosimo and DeFronzo, 2006; Schinzari et al., 2010), acting to increase vasodilation and regulation of vasoconstriction via modulation of nitric oxide and endothelin-1. Conversely, insulin resistance-associated declines in nitric oxide and increases in endothelin-1 activity results in vasoconstriction and reduced blood flow. This process in turn exacerbates both glucose and lipid dysfunction. As a result, increasing insulin resistance and progressive vascular dysfunction work together in a negative feedback loop (Cersosimo and DeFronzo, 2006).

Fifty percent of hypertensive patients are also insulin resistant (Lima et al., 2009). Hypertension impairs neuron-dependent blood flow (known as functional hyperemia) via a number of insulin-resistance related processes including oxidative stress, dysregulation of vasoactive mediators (including nitric oxide and endothelin-1), structural alteration of the

blood vessels, and insufficient cerebral autoregulation (Iadecola and Davisson, 2008). Animal models evidence increased A β deposition with hypertension, which leads to vascular dysfunction and reduced functional hyperemia (Iadecola and Davisson, 2008). In population-based studies, hypertension at mid-life is a risk factor for Alzheimer's disease and vascular dementia, lower brain weight, and A β plaque load (Kivipelto et al., 2001; Launer et al., 2000; Ninomiya et al., 2011; Petrovitch et al., 2000). As with total cholesterol, however, studies examining the effects of late-life hypertension on dementia are mixed, and blood pressure may in fact decline in the years prior to and following clinical dementia diagnosis (Kennelly et al., 2009).

4.4 Obesity

Obesity is a growing and dangerous epidemic in the United States and is closely linked to insulin dysregulation; eighty percent of obese individuals are insulin resistant (Cornier et al., 2008). Insulin typically inhibits adipocyte lipase action, which decreases the release of free fatty acids from adipose tissue. With obesity and insulin resistance, however, this process is disturbed and leads to chronically elevated free fatty acids (Cornier et al., 2008). Free fatty acids are linked to Alzheimer's pathology through a number of potential mechanisms, including inducing inflammation, promoting A β deposition, and inhibiting A β clearance. Elevated free fatty acids inhibit insulin degrading enzyme, which is both essential for normal insulin signaling and vital for A β clearance. (Bravata et al., 2004) Further, free fatty acids promote the development of amyloid and tau filaments *in vitro* (Axen et al., 2003; Bray et al., 2002). Free fatty acids also induce inflammation, particularly through interactions with tumor necrosis factor- α , an inflammatory cytokine that has been implicated in Alzheimer's pathogenesis, particularly A β accumulation in brain (Proietto et al., 1999; Vessby et al., 2001) (López S, 2008). Tumor necrosis factor- α is over-expressed in adipose tissue of obese animals and humans, whereas neutralization of tumor necrosis factor- α increases insulin sensitivity and decreases plasma free fatty acid levels (Piers et al., 2002).

In assessing associations between obesity and dementia, adiposity (and particularly central adiposity) at midlife carries the highest risk for later dementia. Recent pooled risk estimates of a twofold increase in dementia risk for those with a body mass index in the obese range were reported. Midlife obesity is associated with a risk for dementia later in life over and above its association with other insulin-resistance related conditions (Kivipelto et al., 2005; Luchsinger et al., 2008; Whitmer et al., 2008). Evidence concerning the effects of late-life adiposity on dementia risk is less clear, however (Whitmer et al., 2008), and individuals typically begin to lose weight with the onset of dementia. However, a large Spanish study recently demonstrated that overweight and obese nondemented individuals over the age of 65 performed significantly worse across a range of cognitive measures. Despite conflicting literature in this area, however, it is likely that targeting the obesity epidemic in mid-life or before would have substantial beneficial effects on overall health status and cognitive function.

5. NOVEL PHARMACOLOGICAL STRATEGIES

5.1 Intranasal insulin

One innovative therapeutic strategy currently under investigation is the normalization of brain insulin levels through intranasal insulin administration. As reviewed in the previous sections, insulin has pleiotropic effects on pathways implicated in Alzheimer's disease pathogenesis. As such, augmenting central nervous system insulin, in contrast to the majority of therapeutic approaches that focus on narrowly defined mechanisms such as acetylcholine modulation or amyloid accumulation, may have greater potential to impact the clinical symptomatology associated with Alzheimer's disease pathology. Studies administering intravenous insulin while maintaining euglycemia show increased central nervous system insulin and improved cognition (Craft et al., 2003; Craft et al., 1999; Craft et al., 1996; Park et al., 2000). 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 central nervous system insulin levels in persons with Alzheimer's disease 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 central nervous system, bypassing the periphery, via extracellular pathways (Born et al., 2002; Frey, 2002; Thorne et al., 2004). Additionally, an intraneuronal pathway delivers drugs to the central nervous system hours or days later (Baker and Spencer, 1986; Balin et al., 1986; Broadwell and Balin, 1985; Shipley, 1985). Kern et al. (Kern et al., 1999) administered 40 IU of insulin intranasally in young, healthy adults, resulting in increased cerebrospinal fluid insulin levels within 10 minutes of administration compared to placebo with peak levels noted within 30 minutes. Cerebrospinal fluid 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 cerebrospinal fluid are not due to transport from the nasal cavity to systemic circulation. This finding is consistent with a large literature that demonstrates insulin's poor transport from the nasal cavity into blood (Illum, 2002). Although elevated cerebrospinal fluid insulin levels do not conclusively demonstrate that brain insulin levels are similarly elevated, animal studies show labeled intranasal insulin uptake to hippocampus and cortex (Francis et al., 2008). In a murine diabetes model, intranasal insulin reduced brain atrophy and neuronal nuclear factor kappa B activation, while increasing synaptic markers, choline acetyltransferase levels, and activation of Akt, cAMP response element binding protein, and glycogen synthase kinase-3 β . These effects were accompanied by memory enhancement on water maze and radial arm tasks (Francis et al., 2008).

Human functional and cognitive studies of intranasal insulin also support insulin's transport to the central nervous system. Intranasal insulin treatment induced changes in auditory-evoked brain potentials compared to placebo (Kern et al., 1999). Several studies have

reported that two months of daily insulin administration (4×40 international units/day) significantly improves verbal memory and enhanced mood in young healthy adults (Benedict et al., 2004; Benedict et al., 2008; Hallschmid et al., 2008; Stockhorst et al., 2004). In a series of groundbreaking intervention trials, acute and chronic effects of intranasal insulin administration on cognitive function, cerebrospinal fluid biomarkers, and functional positron emission tomography imaging were evaluated in memory impaired older adults. Initial pilot data from these studies showed that intranasal improved verbal memory acutely in persons with Alzheimer's disease or amnesic mild cognitive impairment without affecting plasma insulin or glucose levels, and that 20 international units of insulin produced the greatest benefit (Reger et al., 2006; Reger et al., 2008a). Subsequently, investigation of the chronic effects of 20 international units of intranasal insulin (Reger et al., 2008b) demonstrated that insulin treated subjects had better declarative memory and selective attention performance following 21 days of treatment. In addition, caregivers rated those with greater impairment at baseline as performing significantly better functionally following treatment with insulin, while there was no noted improvement in the placebo group. Fasting plasma insulin and glucose levels were unchanged for both groups, while A β 40/42 ratios increased for intranasal insulin-treated adults compared to placebo, reflecting increased A β 40 relative to A β 42.

A follow up study examined daily intranasal insulin treatment for 4 months in 104 adults with Alzheimer's disease or amnesic mild cognitive impairment, and compared two doses (10 or 20 international units twice per day vs. placebo) (Craft et al., 2011). 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. A scale of general cognitive abilities was also preserved by both doses of intranasal insulin. In exploratory analyses, changes in cerebrospinal fluid A β 42 and tau/A β 42 ratios were associated with cognitive and functional changes for insulin-treated participants. Participants in this trial also underwent positron emission tomography 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/cuneus regions over the 4-month treatment period. The higher dose insulin group showed even greater treatment effects indicating less hypometabolism progression in most regions and in left parietal cortex.

The above results provide compelling evidence that intranasal insulin may benefit adults with amnesic mild cognitive impairment or Alzheimer's disease, and thus may represent a promising novel therapeutic approach to the treatment of degenerative memory disorders. Longer, larger, multi-site trials, currently underway in the United States, will address the question of whether intranasal insulin represents a viable therapeutic approach to the treatment of Alzheimer's disease and mild cognitive impairment.

5.2 Insulin-sensitizing agents: Peroxisome proliferator-activated receptor- γ agonists

Peroxisome proliferator-activated receptor- γ agonists have been shown to improve insulin sensitivity by decreasing circulating insulin and increasing insulin-mediated glucose uptake, with minimal risk of hypoglycemia (Olefsky, 2000). In addition to improving insulin

sensitivity, several investigators have reported that peroxisome proliferator-activated receptor- γ activity may reduce both A β accumulation and inflammatory reactants and protect against neurotoxicity (Combs et al., 2000; Delerive et al., 2001; Landreth, 2007; Paik et al., 2000). Insulin resistance leads to increased central A β levels, peroxisome proliferator-activated receptor- γ agonist therapy may, by decreasing insulin resistance, help to normalize A β levels in brain and to improve associated behavioral symptoms. In vitro, treatment with a low dose of the peroxisome proliferator-activated receptor- γ agonist rosiglitazone increased A β clearance via upregulation of low density lipoprotein receptor-related protein 1 (Moon et al., 2011). Another peroxisome proliferator-activated receptor- γ agonist, pioglitazone, prevented insulin resistance and related increases in A β in fructose-drinking rats (Luo et al., 2011).

Activation of peroxisome proliferator-activated receptor- γ has also been shown to regulate inflammatory responses and apoptosis (Corton et al., 2000; Escher and Wahli, 2000). Peroxisome proliferator-activated receptor- γ agonists inhibit A β stimulated secretion of pro-inflammatory products, arrest the evaluation of activated macrophages, and inhibit the expression of cyclooxygenase-2 (Combs et al., 2000). Decreased oxidative stress and reduced inflammation have been demonstrated with peroxisome proliferator-activated receptor- γ treatment in both in vitro and in vivo models (Hirsch et al., 2003; Schmidt et al., 2003). Rosiglitazone suppressed inflammation in brain cells in vitro (Park et al., 2003) and reversed the negative effects of tumor necrosis factor- α on insulin signaling and insulin-mediated glucose uptake (Hernandez et al., 2004). Animal models suggest that treatment with rosiglitazone significantly reduces inflammation in response to acute injury, and also improves endothelium-dependent vasodilation and coronary arteriole function (Bagi et al., 2004; Cuzzocrea et al., 2004; Tao et al., 2003). Treatment with pioglitazone improved cognitive performance and cerebral glucose metabolism, and reduced oxidative stress in rats treated with intracerebroventricular streptozotocin (Pathan et al., 2006). In humans, non-diabetic patients with cardiovascular disease were treated with rosiglitazone and demonstrated notable peripheral anti-inflammatory effects (Sidhu et al., 2003, 2004). In obese non-diabetic patients, rosiglitazone reduced c-reactive protein, plasma monocyte chemoattractant protein-1, serum amyloid A, and tumor necrosis factor- α ; reductions of c reactive protein and monocyte chemoattractant protein-1 were also noted in the obese diabetic group (Mohanty et al., 2004). These findings suggest that peroxisome proliferator-activated receptor- γ agonists may protect neural tissue from inflammatory damage, and 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 peroxisome proliferator-activated receptor- γ agonist treatment in persons with Alzheimer's disease, results from human clinical trials have been mixed. One trial of rosiglitazone in patients with amnesic mild cognitive impairment and early Alzheimer's disease resulted in improved performance on selective cognitive functions and a more favorable plasma A β 40/42 ratio (Watson et al., 2005). A larger six-month trial failed to yield overall cognitive benefit; however, improvement was noted in subjects without an apolipoprotein E ϵ 4 allele on a task of general cognitive function at the highest dose (Risner et al., 2006). Subsequent phase three clinical trials, however, failed to show any cognitive improvements in patients with mild to

moderate Alzheimer's disease, regardless of genetic status (Gold et al., 2010; Harrington et al., 2011). Pioglitazone has produced similarly mixed results. Treatment with pioglitazone in patients with both type 2 diabetes and Alzheimer's disease 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 (Hanyu et al., 2009; Sato et al., 2011). Follow up data demonstrated that improvements in cognitive function were associated with reduced tumor necrosis factor- α , supporting the anti-inflammatory actions of pioglitazone (Hanyu et al., 2010). However, another trial that was designed to primarily assess the safety of pioglitazone in nondiabetic patients with Alzheimer's disease failed to show any improvements on secondary outcome cognitive and functional measures (Geldmacher et al., 2011).

The inconsistent results from clinical trials using peroxisome proliferator-activated receptor- 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 treatment; however, such safety concerns may nonetheless limit willingness of physicians to prescribe this compound (Mannucci et al., 2010). Interestingly, a recent in vitro model suggested that a subclinical dose of rosiglitazone may produce more beneficial effects on A β clearance than higher doses (Moon et al., 2011). 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 Alzheimer's disease; however, it is possible that treating insulin resistance prior to the onset of clinically significant dementia (e.g, mild cognitive impairment) may produce more favorable cognitive results. Although a few of these trials included patients with amnesic mild cognitive impairment, to date, none have examined the effects of these medications on people with mild cognitive impairment alone. Finally, larger clinical trials utilizing pioglitazone, which seems to have a more favorable safety profile, may help to illuminate whether peroxisome proliferator-activated receptor- γ agonist treatment improves cognitive decline associated with Alzheimer's disease pathological processes.

Conclusions

With an aging population and concurrent rise in chronic health conditions comes a rapid escalation in the incidence of dementia. Although notable strides have been made with regard to discerning the pathophysiological processes associated with Alzheimer's disease and other dementias, pharmacological treatment trials to date have generally produced minimal or disappointing results. Fortunately, many of the processes that underlie the neuropathological features of dementia may be related to risk factors that are responsive to pharmacological interventions, such as insulin resistance and related conditions. Insulin resistance exerts potent negative effects associated with both Alzheimer and vascular pathology. Thus, an important focus will be to identify interventions that effectively target insulin resistance at its early stages, prior to the point at which it exerts its most negative effects on cognition. Innovative therapeutic trials that are currently underway will shed additional light on whether brain insulin resistance can be effectively treated. From a public

health perspective, targeting and treating insulin resistance prior to the presence of clinical symptoms may lead to a drastic reduction in the socioeconomic costs associated with cognitive aging.

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Figure 1.

Consequences of insulin and A β interactions on reduced neuronal insulin receptor signaling and promoting Alzheimer's disease pathology. In type 2 diabetes, there can be decreased or increased levels of insulin in brain (depending on disease state), along with insulin receptor desensitization. A β peptide levels can be enhanced by reduced insulin receptor signaling, and soluble A β oligomers can also block these receptors. Increased A β levels will compete for insulin degrading enzyme with cerebral insulin. A β aggregates can also have direct membrane toxic effect on neuronal cells. Reduced insulin receptor signaling results in reduced phosphoinositide-3 kinase activity that leads to reduced protein kinase B/Akt activity. The consequences of this include reduced glucose metabolism and increased oxidative stress. Specifically reduced glycogen synthase kinase-3 phosphorylation leads to increased tau phosphorylation and A β formation.

Figure 2.

Statistical parametric maps of task-specific activation for (A) normal adults and (B) adults with prediabetes/type 2 diabetes. Maps were constructed by subtracting resting scans from scans obtained while participants performed a memory encoding task. Yellow represents areas of greatest activation.

Figure 3.

Sniffing insulin increases cerebrospinal fluid insulin concentrations in humans (Born et al., 2002). Concentrations of insulin in cerebrospinal fluid before and within 80 min after intranasal administration of human insulin (40 international units; *solid lines*, $n=8$) and placebo (*dashed lines*, $n=5$) Substances were administered with a nasal spray atomizer. *Nose symbol* indicates time of substance administration. Means $\pm$ standard errors are indicated. ** P value smaller than 0.01, * P value smaller than 0.05, for pairwise comparisons of baseline adjusted values between both conditions.