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Insulin Resistance in Alzheimer's Disease

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Abstract

Insulin is a key hormone regulating metabolism. Insulin binding to cell surface insulin receptors engages many signaling intermediates operating in parallel and in series to control glucose, energy, and lipids while also regulating mitogenesis and development. Perturbations in the function of any of these intermediates, which occur in a variety of diseases, cause reduced sensitivity to insulin and insulin resistance with consequent metabolic dysfunction. Chronic inflammation ensues which exacerbates compromised metabolic homeostasis. Since insulin has a key role in learning and memory as well as directly regulating ERK, a kinase required for the type of learning and memory compromised in early Alzheimer's disease (AD), insulin resistance has been identified as a major risk factor for the onset of AD. Animal models of AD or insulin resistance or both demonstrate that AD pathology and impaired insulin signaling form a reciprocal relationship. Of note are human and animal model studies geared toward improving insulin resistance that have led to the identification of the nuclear receptor and transcription factor, peroxisome proliferator-activated receptor gamma (PPAR γ) as an intervention tool for early AD.

Strategic targeting of alternate nodes within the insulin signaling network has revealed disease-stage therapeutic windows in animal models that coalesce with previous and ongoing clinical trial approaches. Thus, exploiting the connection between insulin resistance and AD provides powerful opportunities to delineate therapeutic interventions that slow or block the pathogenesis of AD.

Keywords

Insulin resistance; metabolism; mitochondria; Alzheimer's disease; animal models; cognitive function; ERK; learning and memory; therapeutic windows; PPAR gamma

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Introduction

Hippocampal functional and structural compromise is one of the earliest detectable traits of Alzheimer's disease (AD) (Boeve, 2012; Cavallucci et al., 2012) and is increasingly recognized as an important component of early AD pathology within the recently defined stages of early AD (Huijbers et al., 2014; Peters et al., 2014). The high glucose demand and insulin sensitivity of the hippocampus places it at particular risk for insulin resistance that is quintessential to aging and age-related disease states such as AD (Fehm et al., 2006). Given that the hippocampus is a vital integrator for new memory formation, applying our understanding of the molecular processes underlying hippocampal learning and memory (Sweatt, 2004b; Xia and Storm, 2012) may facilitate the development of therapeutics with disease-modifying efficacy for early AD.

AD is characterized by age-dependent decline in cognition that, in its earliest stages, is the result of amyloid- β ($A\beta$) -mediated dysregulation of a variety of signaling cascades with ERK (extracellular signal-regulated kinase mitogen activated protein kinase) as a central integrator for hippocampal plasticity and memory. In this review, we focus on how insulin resistance may influence early AD cognitive impairment through the role of insulin signaling in hippocampal learning and memory (Figure 1). This review will address the relationships between the insulin and ERK signaling cascades as they relate to learning and memory decline in early AD to explicate a new vision of disease progression and disease stage-specific therapeutic windows (Figure 2).

Insulin signaling

Insulin is the predominant mediator of metabolic homeostasis by regulating glucose, energy, and lipids (Cheng et al., 2010; Shaham et al., 2008). After a meal, elevated glucose causes the pancreas to release insulin which stimulates muscle and adipocytes to take up glucose, thereby reducing plasma glucose. Insulin also regulates development, liver gluconeogenesis, fatty acid synthesis, and mitogenesis (Saltiel and Kahn, 2001; Taguchi and White, 2008). Insulin signals through its cell surface receptor tyrosine kinase that autophosphorylates and recruits adaptor proteins such as insulin receptor substrates 1 and 2 (IRS1, IRS2) (White, 2003) to initiate pleiotropic actions through diverse signaling pathways with ERK serving as a prominent convergence point (Cheng et al., 2010). IRS activates phosphatidylinositol 3-kinase (PI3K) and PDK1 (phosphoinositide-dependent protein kinase-1) activation which then leads to Akt activation (Vadas et al., 2011). Akt is a central integrator of insulin signaling by sensing energy status, oxygen availability and growth factors to balance feeding-dependent lipogenesis with fasting-dependent gluconeogenesis through many signaling intermediates. For example, Akt drives GLUT (glucose transporter) plasma membrane translocation to normalize blood glucose and activates GSK-3 β (glycogen synthase kinase-3 β) to induce glycogen synthesis through the target of rapamycin complexes, including mTOR (mammalian target of rapamycin), to control AMPK, energy metabolism, mitochondrial function, synaptic plasticity and memory (Cheng et al., 2010; Kleinriders et al., 2014; Stoica et al., 2011; White, 2003). Akt also regulates mitochondrial function through FOXO-1 (forkhead box O-1) (Fernandez and Torres-Aleman, 2012), a transcription factor controlling expression of genes in the electron transport chain for

mitochondrial integration of glucose and lipid metabolism (Fernandez and Torres-Aleman, 2012). Mitochondria perform this essential balance by coupling the TCA cycle with oxidative phosphorylation. Through the ERK/CREB/CBP (mitogen activated protein kinase/cyclic-AMP response element binding protein/CREB binding protein) pathway, insulin controls mitogenesis and differentiation through transcriptional and translational mechanisms including AMPK-dependent energy homeostasis. Many of these downstream signaling mediators contribute to insulin resistance through feedback inhibition of IRS through serine phosphorylation providing a variety of pathways toward compromise of insulin signaling and subsequent insulin resistance.

Insulin resistance and metabolic stress

The molecular mechanisms of insulin signaling and insulin resistance have been extensively delineated (Biddinger and Kahn, 2006; Samuel and Shulman, 2012). In brief, insulin resistance induces metabolic stress that manifests as altered mitochondrial function and chronic inflammation that further exacerbate metabolic homeostasis in part through lipid (Iwen et al., 2014) and A β metabolism (Farris et al., 2003) leading to the inability to properly respond to insulin (insulin resistance), typified by hyperinsulinemia, hyperglycemia, and hyperlipidemia (Lowell and Shulman, 2005; Turner and Heilbronn, 2008) that drives the metabolic syndrome and diseases such as type 2 diabetes, obesity, cardiovascular disease, chronic inflammation, and neurodegeneration.

At the subcellular level, insulin resistance is characterized by mitochondrial dysfunction and loss of proper glucose and lipid metabolism through the TCA cycle and oxidative phosphorylation to ultimately regulate the electron transport chain which controls energy production (Saltiel and Kahn, 2001). Critical molecular functions regulating mitochondrial activity include ATP synthesis and transport, solute and protein transport, reduction-oxidation (redox) balance, in addition to homeostatic anabolism and catabolism. Perturbations of these mitochondrial functions at a variety of loci are the molecular metabolic consequences of insulin resistance.

Insulin and amyloid- β metabolism

Insulin resistance and A β metabolism are mechanistically related in a compelling manner that has relevance to AD. Elevated A β induces removal of cell surface insulin receptors furthering insulin resistance (De Felice et al., 2009; Zhao et al., 2008). Insulin also affects A β production and clearance via the MEK-ERK pathway (Gasparini et al., 2001), thereby affecting net accumulation in the brain that, in turn, is regulated in a highly integrated fashion by APP (amyloid precursor protein) (Rohe et al., 2009), SORLA (Buggia-Prevot and Thinakaran, 2014; Rohe et al., 2009), Rabs (Udayar et al., 2013), AMPK (Tillu et al., 2012), and ApoE (apolipoprotein epsilon) (Bales et al., 1999; Holtzman et al., 2000; Strittmatter et al., 1993). For example, ApoE directly regulates binding and degradation of A β (Jiang et al., 2008) while reducing brain insulin signaling and glucose thereby leading to elevated brain insulin (Ong et al., 2014). ApoE plays a key role as a carrier for cholesterol clearance (Pfrieger and Ungerer, 2011), regulates cholesterol metabolism which is a causative factor in the insulin resistance of diabetes (Lee et al., 2012), and inversely influences A β clearance (Wildsmith et al., 2013), thus illustrating the highly integrated and potentially reiterative

nature of insulin signaling and A β metabolism that can feed forward into dysfunctional insulin signaling and cognitive decline.

Lifestyle risk factors for insulin resistance and Alzheimer's disease

A variety of risk factors have been identified for the development of insulin resistance including stress, obesity, arthritis, brain injury, diet, sleep, education, and physical and social activity (Mowery et al., 2009; Samson and Garber, 2014). For example, cardiovascular disease, as exemplified by high blood pressure, heart disease, stroke, and high cholesterol (Luchsinger et al., 2004; Szekely et al., 2007), are significant risk factors for LOAD as vascular damage is increasingly appreciated as contributing to the cognitive impairment profile associated with early AD (Lee, 1994; Sparks et al., 1994; Sparks et al., 1995). More recently, chronic metabolic disorders such as gluco-regulatory abnormalities and insulin resistance quintessential of type 2 diabetes have been recognized as significantly contributing to LOAD risk (Arvanitakis et al., 2004; Craft, 2009; Patterson et al., 2008; Sperling et al., 2011; Stockhorst et al., 2004). Chronic inflammation is a common denominator in many of these conditions that contribute to risk for insulin resistance as well as AD dementia (De Felice and Ferreira, 2014; Ferreira et al., 2014; Sutinen et al., 2012). Furthermore, a normal consequence of aging is loss of insulin sensitivity that can progress to insulin resistance depending on comorbid lifestyle factors (Leon-Latre et al., 2014). That traumatic brain injury stimulates A β production and causes insulin resistance where insulin sensitizers provide symptomatic relief (Ley et al., 2011; Mowery et al., 2009) supports the notion established in animal models for AD-like amyloidosis that aberrant production and accumulation of A β can induce insulin resistance that contributes to cognitive deficits (Pedersen and Flynn, 2004; Rodriguez-Rivera et al., 2011). Human genetics, including ethnicity, also play a key role in contributing to insulin resistance (Hashimoto et al., 1994; Thies et al., 2013) and therefore to AD risk. Nonetheless, the poorly understood mechanisms underlying the combined risk of genetic and environmental factors are considered to underlie the majority of LOAD (Tsatsoulis et al., 2013).

Molecular mechanisms of inflammation-mediated insulin resistance

Chronic elevated blood glucose induces inflammation and can precipitate insulin resistance. Proinflammatory mediators such as TNF- α , IL-1- β , and IL-6 create the inflammatory milieu that reduce insulin sensitivity by feedback inhibition of the insulin receptor and, through a feed-forward mechanism, perturb mitochondrial function to stimulate reactive oxygen species production to further the inflammatory state (Bonnard et al., 2008; Cheng et al., 2010; Hoeks and Schrauwen, 2012; Idriss and Naismith, 2000). Such a chronic inflammatory environment can increase NF κ -B-inducing kinase (NIK), which independently compromises mitochondrial function to further promote insulin resistance (Choudhary et al., 2011; Sheng et al., 2012). Neuroinflammation is precipitated both by peripheral immune cells and proinflammatory cytokines secreted into the blood during chronic hyperglycemia that cross the blood-brain barrier in addition to inflammatory cytokine production within the brain innate immune system (McGeer and McGeer, 2010).

Neuroinflammation, a field in its infancy (McGeer and McGeer, 2010), aggravates neurological disorders, exacerbating the accompanying cognitive deficits (Chen et al., 2008;

Corona et al., 2012). Feed-forward neuroinflammation accelerates the progression of neurological diseases to neurodegenerative disease due to the release of neurotoxic substances (Craft et al., 2005) and proinflammatory cytokines (Swardfager et al., 2010) from the CNS innate immune system. Recent work suggests that soluble misfolded A β can induce inflammatory cytokines (e.g., TNF- α) through a NIK-dependent pathway (Akama and Van Eldik, 2000; Carrero et al., 2012) suggesting that A β contributes to brain insulin resistance (Talbot et al., 2012) in addition to its established role in synaptic toxicity during early AD (Hardy, 2009; Walsh and Selkoe, 2004).

Insulin in learning and memory

Insulin is secreted from the β -cells of the pancreas to maintain glucose homeostasis in the periphery, although insulin also plays a profound role in brain metabolism and cognition. Accumulating evidence indicates that insulin signaling in the brain impinges upon the ERK signal transduction cascade for hippocampal synaptic plasticity, learning and memory through the maintenance of proper redox, inflammatory, lipid, and glucose homeostasis within neural networks. Several lines of evidence support the model that excess A β mediates the association between insulin resistance and cognitive impairment in early AD and, due to the heightened metabolic and energy needs of this brain region, the hippocampus is particularly vulnerable to these processes in early AD (Bosco et al., 2011; Cholerton et al., 2011; Herrup et al., 2013; Schioth et al., 2012).

ERK in learning and memory

In the hippocampus, the ERK cascade is essential to the induction and maintenance of long term potentiation (LTP) and memory consolidation as it converges with a number of other signaling cascades, including CaMKII, PKA, and PKC (Kelleher et al., 2004; Sweatt, 2001; Sweatt, 2004a) and can be activated by a number of receptors and second messenger systems involved in cell homeostasis including the insulin receptor, a tyrosine kinase (RTK), and downstream pathways (Bell et al., 2004). In the canonical ERK pathway (Sweatt, 2001; Sweatt, 2004a), peptide growth factors and hormones (e.g., insulin) bind to their respective RTKs leading to several phosphorylation and translocation events that lead to guanine nucleotide exchange factor activation and GDP-GTP exchange on the small G protein Ras. Active Ras then recruits the serine/threonine kinase Raf to the cell membrane, where it is activated and phosphorylates the dual specificity kinase MEK. MEK then binds to and dually phosphorylates ERK to initiate a number of downstream effects, including the phosphorylation-dependent activation of kinases and transcription factors that induce memory consolidation-dependent gene expression (Giovannini et al., 2001; Wang et al., 2003; Winder et al., 1999), and the facilitation of protein synthesis and the remodeling or stabilization of dendritic spines (Goldin and Segal, 2003; Lynch, 2004; Sweatt, 2004a; Wu et al., 2001) necessary for LTP and memory.

The requirement for ERK activation in LTP and hippocampus-dependent learning was established by demonstrating that its inhibition by MEK inhibitors such as PD098059, SL327, or U0126 blocked these processes (Atkins et al., 1998; Selcher et al., 1999; Winder et al., 1999). More detailed analyses found that high frequency stimulation of the Schaffer collateral inputs to the hippocampal CA1 region selectively activated the p42 isoform of

ERK (English and Sweatt, 1996; English and Sweatt, 1997), and that the p42 isoform (heretofore referred to as 'ERK2') is activated following training in a hippocampus-dependent cognitive task (Atkins et al., 1998). Furthermore, knockout mice in which the p44 isoform of ERK (ERK1) was deleted do not exhibit hippocampal LTP deficits or impairment in hippocampus-dependent memory formation (Selcher et al., 2001). Since ERK is fundamental to cellular homeostasis, it poses significant challenges as a therapeutic target. It is therefore imperative that we apply our understanding of the molecular processes of learning and memory to early AD pathophysiology to identify components of this highly integrated signaling network as viable therapeutic targets.

Alzheimer's disease

Alzheimer's disease pathogenesis

The aging and dementia research community has made significant progress in the past 25 years by identifying causative genes and risk factors as well as characterizing the clinical and pathologic features of AD (Thies et al., 2013). These findings led to a reconceptualization of AD as having a long preclinical phase during which significant pathology is present prior to clinically significant cognitive impairment (Caselli and Reiman, 2013; McKhann et al., 2011; Reiman et al., 2011; Sperling et al., 2011). This preclinical phase is followed by two additional stages termed mild cognitive impairment (MCI) due to AD and dementia due to AD that now have new diagnostic and biomarker criteria (Albert et al., 2011; Jack et al., 2011a; Jack and Holtzman, 2013; Jack et al., 2011b; McKhann et al., 2011; Sperling et al., 2011). The quintessential pathological hallmarks of AD are accumulation of A β in plaques and hyperphosphorylated tau in neurofibrillary tangles (Jack and Holtzman, 2013). However, in the past decade or so, oligomeric forms of A β have been implicated as the culprit initiating AD and an emerging concept in AD pathophysiology is that while A β oligomers trigger disease, misfolded tau is requisite for full neurotoxicity (Jack and Holtzman, 2013; Musiek and Holtzman, 2012). In any case, these oligomers induce neuroinflammation that contributes to insulin resistance.

Risk factors for Alzheimer's disease

Cases of AD are categorized as either inherited early-onset or sporadic LOAD, with the overwhelming majority (>95%) of cases qualifying as LOAD. Early-onset, familial AD describes individuals who develop AD before the age of 65 due to the inheritance of autosomal dominant gene mutations with symptoms occasionally appearing as early as 30 years of age. The known risk genes for the development of AD that have been identified include autosomal dominant mutations in APP, presenilin 1 (PS-1) and presenilin 2 (PS-2). The risk of developing LOAD is thought to arise due to interactions between inherited and environmental risk factors that function in an age-dependent manner (Mayeux and Stern, 2012; Reitz and Mayeux, 2014). Inheritance of APOE-4 is the most significant risk factor for LOAD (Sadigh-Eteghad et al., 2012). Individuals who carry two copies of the ϵ 4 allele have a higher risk than those who carry only one copy, and both groups have a higher risk than those who carry only the ϵ 2 or ϵ 3 forms (Slooter et al., 1998). While the exact reason for increased risk is unclear, it is known that APOE enhances proteolytic clearance of A β and that the ϵ 4 variant is associated with less efficient clearance than the ϵ 2 or ϵ 3 isoforms

(Jiang et al., 2008). It is noteworthy that being an APOE-4 carrier does not guarantee development of AD, and lacking APOE-4 is not preventative, suggesting that factors in addition to A β burden have significant impact on LOAD susceptibility.

Insulin resistance in Alzheimer's disease

Type 2 diabetes is a chronic metabolic disorder characterized by peripheral insulin resistance, hyperglycemia, and hyperinsulinemia (Baker et al., 2011; Matsuzaki et al., 2010). Epidemiological studies consistently link type 2 diabetes, as well as intermediate stages of insulin resistance, with increased risk of developing AD (Akomolafe et al., 2006; Arvanitakis et al., 2004; Hofman et al., 1997; Luchsinger et al., 2004; Luchsinger et al., 2001; Ott et al., 1999; Rivera et al., 2005; Schrijvers et al., 2010; Watson and Craft, 2003; Xu et al., 2004). Chronic type 2 diabetics have up to a 65% increased risk of developing AD (Arvanitakis et al., 2004). Furthermore, clinical studies have found evidence for central insulin resistance in the AD brain (Craft et al., 1998; Talbot et al., 2012) as well as dysregulated glucose metabolism and peripheral insulin resistance in AD patients (Craft et al., 1999a). Thus, impaired insulin signaling is strongly linked to AD pathology (Craft et al., 2013; van Himbergen et al., 2012).

The link between these two disease states may be based upon the role of insulin in brain metabolism and plasticity (Kleinridders et al., 2014). Insulin receptors are widely distributed in brain regions known to be involved in memory function, including high concentrations at synapses in the hippocampus and amygdala, and moderate expression in cortex and cerebellum (Werther et al., 1987). Insulin readily crosses the blood-brain barrier in order to regulate glucose utilization (Woods et al., 2003) and this process influences amyloid, neuronal survival, energy metabolism, and neural network plasticity (Craft et al., 2003; Craft and Watson, 2004; Park et al., 2000; Wallum et al., 1987; Wickelgren, 1998). Furthermore, acute insulin administration improves memory in both humans and rodents (Craft et al., 2012; Park et al., 2000; Watson et al., 2006), and disruption of CNS insulin signaling leads to cognitive deficits in rodents (Lannert and Hoyer, 1998; Steen et al., 2005). Subsequent studies in animal models for insulin resistance, AD, or both, have established that insulin resistance exacerbates A β and tau phenotypes including enhanced A β 42/40 ratio, total tau, and hyperphosphorylated tau (Ho et al., 2004; Lester-Coll et al., 2006; Li et al., 2007; Masciopinto et al., 2012; Plaschke et al., 2010; Qu et al., 2011; Searcy et al., 2012; Takeda et al., 2010) and AD amyloidosis models exhibit insulin resistance (Rodriguez-Rivera et al., 2011).

Insulin sensitizers prescribed for diabetes include the TZDs RSG (rosiglitazone) and PIO (pioglitazone) that target the nuclear receptor and transcription factor PPAR γ , and the biguanide MFM that targets AMPK. Activation of PPAR γ with RSG in the Tg2576 mouse model of AD facilitates hippocampus-dependent memory consolidation and leads to induction of genes regulated by promoters with PPREs (PPAR γ response elements) and CREs (cyclic-AMP response elements) (Denner et al., 2012), the latter of which are prototypically regulated by CREB (cyclic AMP response element binding protein) and CBP (CREB binding protein) transcription factors. Upstream from these memory consolidation gene transcription events is the common integrator of insulin signaling pERK, which is

recruited to PPAR γ during consolidation (Jahrling et al., 2014) and requisite for hippocampal learning and memory (Sweatt, 2001; Sweatt, 2004a). Thus, targeting the insulin signaling pathway during early AD cognitive impairment represents a viable therapeutic opportunity based upon solid empirical evidence that insulin resistance, AD pathology and related cognitive decline are mechanistically interrelated.

Animal models reveal reciprocity between insulin resistance and Alzheimer's disease pathology

The criteria for staging and diagnosis of AD were recently revised to reflect new knowledge regarding biomarker profiles for the disease. With refinement of clinical staging comes the realization that many of the mechanistically-conceived animal models are more representative of preclinical AD and possibly MCI (Ferretti et al., 2011; Hernandez et al., 2010) which is consistent with the finding that recent AD clinical trials using the insulin sensitizing TZDs (RSG, PIO) that target PPAR γ mainly provide cognitive benefit during early stage AD (Craft, 2012; Gold et al., 2010; Hanyu et al., 2009; Risner et al., 2006; Sato et al., 2011; Watson et al., 2005). Thus, animal models may provide vital predictive power to future clinical trials by informing upon the disease stage profile that best matches a particular therapeutic intervention.

While genetic mouse models of AD do not fully recapitulate the entire spectrum of the human disease, these models have been integral to furthering our understanding of early disease pathology and have been invaluable for the study of disease mechanisms and testing of potential therapeutic strategies. Since the known gene mutations that cause familial AD produce congruent pathology observed in LOAD, many of these models express human transgenes containing mutations associated with familial AD (Bales, 2012; Hsiao, 1998; Sabbagh et al., 2013). As such, there are a number of transgenic mouse models of AD, including those that lead to aberrant processing and accumulation of A β (Tg2576, PDAPP, presenilin conditional KO/APP, PS1/APP, CRND8, PGDF-APPSW) and mutant tau for neurofibrillary tangle formation (P301S, rTg4510, 3 $\times$ Tg-AD, 5 $\times$ Tg-AD). All of these models exhibit age-dependent cognitive decline in a variety of behavioral paradigms (Webster et al., 2014) including fear conditioning, Morris water maze, and radial arm maze, behaviors all requiring proper hippocampal function, a brain region particularly susceptible to the earliest stages of AD including the newly defined preclinical stage of AD (Huijbers et al., 2014; Peters et al., 2014).

Neuroinflammation and insulin resistance, as well as dysregulated mitochondrial function and cholesterol metabolism, are common to several chronic diseases, such as obesity, type 2 diabetes, metabolic syndrome, cancer, and cardiovascular diseases (Hirabara et al., 2012). Dysregulation of these important homeostatic processes are also hallmarks of AD (Schrijvers et al., 2010; Talbot et al., 2012). Here we discuss studies using the Tg2576 mouse model for AD that have helped elucidate how these processes contribute to hippocampal dysfunction and cognitive impairment of early AD. While the extant literature contains several examples of alternative models for AD and insulin resistance (Park, 2011), the most comprehensive body of work on this subject is encompassed by Tg2576. Thus, a suitable model for examining the mechanisms underlying cognitive deficits due to aberrant

accumulation of A β prior to the onset of overt neuropathology, providing an opportunity to study a model similar to early stage human AD (Hsiao et al., 1996).

Tg2576 mice express human APP₆₉₅ containing the familial 'Swedish' mutation (Lys670Asn670, Met671Leu671) (Hsiao et al., 1996) that leads to elevated A β by 2MO, and exhibit age-dependent accumulation of misfolded A β leading to plaque formation by ~12MO. Accumulation of misfolded oligomeric forms of soluble A β is believed to be responsible for the AD-related hippocampal synaptic and cognitive dysfunction that manifests at 5-6MO (Dineley et al., 2007; Dineley et al., 2002; Hsiao et al., 1996; Kawarabayashi et al., 2001; Lesne et al., 2006; Nenov et al., 2014; Pirttimaki et al., 2013; Taglialatela et al., 2009). While Tg2576 do not form neurofibrillary tangles, they do accumulate oligomeric tau by 5MO, which recent work has suggested represents the toxic species that furthers cognitive decline (Castillo-Carranza et al., 2014; Lasagna-Reeves et al., 2012). Tg2576 also do not portray overt neurodegeneration yet Tg2576 exhibit synapse and volume loss in the hippocampus (Hernandez et al., 2010; Irizarry et al., 1997) which is considered one of the best correlates to cognitive impairment of early, and possibly preclinical, AD (Albert et al., 2011; Cavallucci et al., 2012; Sperling et al., 2011). Furthermore, Tg2576 possess dysregulated hippocampal ERK (Dineley et al., 2001), impaired recognition memory, and deficits in ERK-dependent episodic, associative, and spatial learning and memory (Dineley et al., 2007; Dineley et al., 2002; Taglialatela et al., 2009; Westerman et al., 2002), all correlates of the cognitive deficits identified in early AD in humans (Hamann et al., 2002; Hoefer et al., 2008; Hort et al., 2007). Based on these observations and the current biomarker criteria, Tg2576 and related models approximate the pathological transition from preclinical AD to MCI and are well-suited to pursue identification of early biomarkers of disease and the examination of therapeutic interventions to enhance synaptic and cognitive function rather than reversing neuronal loss due to the advanced neuropathology of AD.

Neuroinflammation

Neuroinflammation, triggered by elevated A β , can directly lead to increased TNF- α and impaired synaptic plasticity, learning and memory (Sims-Robinson et al., 2010). Thus, A β -mediated CNS inflammatory responses are thought to contribute to cognitive decline and neurodegeneration in AD (McCoy and Tansey, 2008). Previous studies on aged (>12MO) Tg2576 brains detected TNF- α , IL-6, and IL-1 β positive astrocytes surrounding plaque deposits (Benzing et al., 1999; Mehlhorn et al., 2000). The local immune response detected around cortical A β deposits in Tg2576 mouse brain is seemingly different to that observed in brains from AD patients but may represent an initial event of chronic neuroinflammation. However, since the full scope of elevated cytokines found in AD brains are lacking in aged Tg2576 brain may reflect differences in the murine neuroinflammatory process and may explain why mouse models for A β amyloidosis fail to progress to overt neurodegeneration. Nonetheless, Tg2576 neuroinflammation is presumed to be triggered by soluble misfolded A β as shown in vitro (Akama and Van Eldik, 2000; Carrero et al., 2012) further suggesting that A β contributes to brain insulin resistance (Talbot et al., 2012) in addition to its established role in synaptic toxicity during early AD (Hardy, 2009; Walsh and Selkoe, 2004).

Mitochondrial dysfunction

Mitochondrial function is compromised by insulin resistance and accompanying inflammation (Bonnard et al., 2008; Hoeks and Schrauwen, 2012). Tg2576 exhibit both insulin resistance and altered mitochondrial proteins wherein cognitive enhancement with PPAR γ agonism is accompanied by normalization of these proteins critical to energy and metabolism including ATP production, mitochondrial membrane potential and transport dynamics, and redox balance (Denner et al., 2012). These discoveries are consistent with previous reports that mitochondrial dysfunction contributes to cognitive impairment and that both can be ameliorated with PPAR γ agonism (Baliatti et al., 2013; Gong et al., 2013). Again, these findings dovetail with current thinking that neuroinflammation-induced insulin resistance and mitochondrial dysfunction are interrelated and contribute to the molecular pathogenesis of AD cognitive decline (Bosco et al., 2011).

Central insulin resistance

Insulin signaling in the brain and its impact on metabolism and function are similar to those established in the periphery (Kleinridders et al., 2014). Diet-induced insulin resistance leads to down-regulation of insulin receptor signaling in the brain of insulin-resistant Tg2576 mice and is associated with decreased AKT/PKB activity leading to GSK-3 activation (Ho et al., 2004). Similar outcomes have been reported for alternative AD transgenic models (Bhat and Thirumangalakudi, 2013; Mody et al., 2011).

In humans, a key feature of insulin resistance in type 2 diabetes is phosphorylation of IRS-1 at serine residues. IRS-1 serine phosphorylation results from feedback and feed forward inhibition exerted by several kinases including ERK2 and mTOR (Boura-Halfon and Zick, 2009; Gual et al., 2005; Sun and Liu, 2009; Tanti and Jager, 2009). For example, IRS-1 Ser616 phosphorylation is important because it has been reported to show the best positive correlation with amyloid oligomers and the best inverse correlation in humans with episodic memory deficits in MCI and AD (Talbot et al., 2012). Further, IRS-1 Ser616 hyperphosphorylation is consistent with previous work on APP transgenic mice of a similar age (Long-Smith et al., 2013; Yarchoan et al., 2014).

Early studies found that diet-induced insulin resistance promotes AD pathology and exacerbates cognitive deficits in Tg2576 (Goldstein et al., 2007; Ho et al., 2004). Coincident work revealed that Tg2576 manifest peripheral insulin resistance in an age-dependent manner in the absence of diet manipulations (Pedersen and Flynn, 2004). Our evaluation of Tg2576 for insulin resistance assessed peripheral insulin and glucose regulation by directly measuring serum insulin and glucose as well as performing the fasting glucose tolerance test (Rodriguez-Rivera et al., 2011). These measures showed that 5MO Tg2576 are normoglycemic and normoinsulinemic with the emergence of peripheral insulin resistance and hyperinsulinemia by 9MO. We previously reported that 9MO Tg2576 respond to cognitive enhancement with the PPAR γ agonist and insulin sensitizer RSG while 13MO Tg2576 are unresponsive to this intervention (Denner et al., 2012; Rodriguez-Rivera et al., 2011). This suggests that a different aspect of the insulin signaling pathway might be exploited during more severe cognitive impairment.

In the periphery, AMPK is a key cellular sensor of reduced energy supply and is an additional therapeutic target in diabetes to increase insulin sensitivity. Although little is known of AMPK function and regulation in the CNS, it is implicated in AD and evidence shows that neuronal AMPK regulates ERK (Ali and Fonseca, 2012; Salminen et al., 2011). Insulin resistance leads to down-regulation of AMPK in the periphery (Saha et al., 2010) and is a negative regulator of ERK activity in neurons (Tillu et al., 2012) which is consistent with our previous observations of hyperactive ERK in 13MO Tg2576 hippocampus (Dineley et al., 2001). In these contexts, it will be important to pursue additional treatment strategies during the age-dependent cognitive decline to fully understand the potential value of AMPK as a therapeutic target. Finally, these observations support our overall hypothesis that proper ERK dynamic range is imperative for proper cognitive performance and determines efficacy of therapeutic interventions that target hippocampal cognitive function.

In summary, studies in animal models for insulin resistance, AD, or both, have established that insulin resistance exacerbates A β and tau phenotypes including enhanced A β 42/40 ratio, total tau, and hyperphosphorylated tau (Bhat and Thirumangalakudi, 2013; Li et al., 2012; Plaschke et al., 2010; Qu et al., 2011; Searcy et al., 2012). These and other mechanistic similarities have led the medical community to list insulin resistance as a risk factor for the development of AD (Kloppenborg et al., 2008). Furthermore, clinical evidence demonstrates decreased central insulin sensitivity in non-diabetic AD brains (Craft et al., 1998; Talbot et al., 2012) as well as dysregulated glucose metabolism and insulin resistance in non-diabetic AD patients (Craft et al., 1999b), suggesting that AD pathology and impaired insulin signaling form a reciprocal relationship. This reciprocity is supported by animal studies in which manipulations that induce insulin resistance promote AD pathology (Lester-Coll et al., 2006; Li et al., 2012) and AD amyloidosis models exhibit insulin resistance (Rodriguez-Rivera et al., 2011).

Therapeutic Opportunities

Targeting insulin resistance to enhance cognition in Alzheimer's disease

Because insulin sensitizers improve insulin resistance in diabetes, they have also been tested for cognitive improvement in AD. Several previous large-scale clinical trials testing insulin sensitizers for AD failed to show efficacy, similar to the failure of many other AD drug candidates (Becker and Greig, 2013; Holland et al., 2012). However, it is now apparent that failure of these many trials is potentially due to poor trial design such as treatment cohorts that included a predominance of late-stage AD, failure to demonstrate cholinesterase efficacy, short treatment regimen, and no biomarker assessment (Becker and Greig, 2013; Holland et al., 2012). In contrast, small trials on patients diagnosed as MCI/early AD have consistently shown that insulin sensitizers provide significant cognitive benefit (Craft, 2012; Gold et al., 2010; Hanyu et al., 2009; Risner et al., 2006; Sato et al., 2011; Watson et al., 2005).

Like insulin, insulin sensitizers appear to impinge upon components of the insulin signaling axis and expression of genes that affect the neuropsychological profile of cognitive enhancement in MCI and early AD (Craft and Watson, 2004). As such, there is renewed interest in targeting the insulin signaling pathway (Crenshaw et al., 2013) as PIO is currently

in an ongoing clinical trial (“Biomarker Qualification for Risk of Mild Cognitive Impairment Due to Alzheimer's Disease and Safety and Efficacy Evaluation of Pioglitazone in Delaying Its Onset;” www.clinicaltrials.gov/ct2/show/NCT01931566?term=Alzheimer%27s+AND+pioglitazone&rank=1; sponsored by Takeda). MFM is also currently in a clinical trial for patients diagnosed as MCI/early AD (“Effect of Insulin Sensitizer Metformin on AD Biomarkers;” sponsored by the University of Pennsylvania; www.clinicaltrials.gov/ct2/show/NCT01965756?term=Alzheimer%27s+AND+metformin&rank=2). An additional consideration that we put forth here is that, based upon the preclinical mouse models for AD amyloidosis, insulin resistance and biomarker status may define therapeutic windows to predict clinical efficacy of insulin and insulin sensitizer therapies.

PPAR γ as a therapeutic target for Alzheimer's disease

PPARs can be endogenously activated by free fatty acids and the eicosanoids, derivatives of omega-3 and omega-6 fatty acids. Pharmacologically, PPAR γ is activated by members of the highly selective TZD drug class. While early research focused on the role of PPAR γ in peripheral tissues (Desvergne and Wahli, 1999), roles in neuronal function emerged following immunohistological identification of PPAR γ expression in brain areas associated with higher cognitive function, including the cortex, basal ganglia, hypothalamus, and hippocampus (Inestrosa et al., 2005; Moreno et al., 2004; Sarruf et al., 2009). PPAR γ agonism is generally recognized as neuroprotective (Breidert et al., 2002; Feinstein, 2003; Hyong et al., 2008; Victor et al., 2006) via attenuated levels of pro-inflammatory proteins (e.g. iNOS, TNF α , MMP9), reactive oxygen species (ROS), and A β . Currently, PPAR γ is a therapeutic target in many CNS disease states including Parkinson's disease (Barbiero et al., 2014; Pisanu et al., 2014; Ridder and Schwaninger, 2012), ischemia-reperfusion injury (Gele et al., 2014; Singh et al., 2014), and traumatic brain injury (Sauerbeck et al., 2011; Thal et al., 2011).

Since PPAR γ maintains 99% similarity and 95% identity between humans and mice (Fajas et al., 1997), transgenic mouse models based upon APP and/or PS-1 and/or tau have provided an excellent system in which to examine the effects of PPAR γ agonism on AD pathology *in vivo*. PPAR γ agonism produces similar outcomes in these models suggesting commonality of PPAR γ mechanisms. For example, hippocampal insulin signaling, energy metabolism, and AMPK function, are similarly dysregulated in an APP/PS1 model (Pedros et al., 2014). Using PPAR γ agonists, we and others have demonstrated that PPAR γ agonism improves cognitive performance in these AD mouse models, predominantly in tasks that require intact hippocampal ERK signaling (Escribano et al., 2009; O'Reilly and Lynch, 2012; Pedersen et al., 2006; Rodriguez-Rivera et al., 2011). Cognitive enhancement has been shown to be accompanied by improved AD biomarker profiles: alleviation of amyloid and tau pathology (Escribano et al., 2010; Jiang et al., 2012; Kummer et al., 2014; Mandrekar-Colucci et al., 2012; O'Reilly and Lynch, 2012), reduced neuroinflammation (Escribano et al., 2010; Prakash and Kumar, 2014; Yin et al., 2013), increased antioxidant protection (Nicolakakis et al., 2008; Yin et al., 2013), amelioration of central insulin resistance (Masciopinto et al., 2012; Yin et al., 2013), and normalization of several transcripts and proteins related to ERK and insulin signaling in the hippocampus, including

reversal of down-regulated PPAR γ (Denner et al., 2012). The latter mechanism reinforces the notion that modulators of ERK activity are promising therapeutic targets for early AD intervention.

Mechanisms of PPAR γ cognitive enhancement

Alleviation of amyloid pathology has been attributed to mechanisms involving enhanced A β clearance (Mandrekar-Colucci et al., 2012), suppressed expression of β -secretase and APP (Dobrowolska et al., 2014), as well as enhanced APP ubiquitination and subsequent degradation (Lonskaya et al., 2014). Work in vitro has demonstrated that TZD PPAR γ agonism reduced A β accumulation (Camacho et al., 2004) and the expression of TNF α and interleukin-6, thereby decreasing A β -mediated inflammation (Combs et al., 2000), factors that also contribute to insulin resistance. Furthermore, application of A β to hippocampal slice cultures has been shown to inhibit Schaffer-collateral LTP, while TZD pre-treatment attenuated this effect and irreversible antagonists of PPAR γ reversed it (Costello et al., 2005). Taken together, these data suggest a therapeutic role for PPAR γ agonism to combat AD pathology in order to ameliorate associated network plasticity and cognitive deficits.

Hippocampal network excitability has recently been proposed as a confounding factor resulting from AD amyloidosis in mice and humans (Palop et al., 2007; Palop and Mucke, 2009; Putcha et al., 2011; Vossel et al., 2013). To further delineate molecular mechanisms of PPAR γ agonism-mediated cognitive enhancement, we assessed whether PPAR γ agonism alleviated altered spontaneous and evoked excitatory synaptic transmission at the entorhinal cortex to dentate gyrus synapse in the hippocampus. We found that dentate gyrus hyperactivity was due to a presynaptic mechanism that was normalized by PPAR γ agonism (Nenov et al., 2014). Proteomic analysis of Tg2576 dentate gyrus proteins indicated that PPAR γ agonism resulted in the induction of presynaptic neurotransmitter vesicle proteins (SNAREs) that contained both PPREs and CREs in the promoters of RSG-regulated gene transcripts and proteins (Nenov et al., 2014), pointing again to a compelling interrelationship between PPAR γ and ERK in the hippocampus of a preclinical AD model.

Multiprotein complexes allow rapid, fine-tuned responses to mediate signal integration and processing of diverse information to affect cellular responses that underlie physiological processes such as memory consolidation. While we remain largely ignorant of CNS ERK multiprotein complexes, in the periphery, ERK forms a central node in multiprotein complexes comprised of upstream and downstream modulators to execute substrate recruitment and subsequent new gene transcription. ERK multiprotein complexes are commonly found to contain nuclear receptors such as PPAR γ (Wortzel and Seger, 2011). Our bioinformatics analyses of proteomic and transcriptomic studies suggested the hippocampal ERK and PPAR γ signaling axes converge to drive RSG-mediated cognitive enhancement in Tg2576 (Denner et al., 2012). Indeed, we found that PPAR γ directly binds to pERK in multiprotein complexes that are required for memory consolidation (Jahrling et al., 2014). Furthermore, the pERK-PPAR γ complexes were found in humans with AD and the severity of disease inversely correlated with the amount of complexes in the hippocampus suggesting that PPAR γ association with pERK is indicative of cognitive reserve (Jahrling et al., 2014). Thus, PPAR γ agonism contributes to cognitive enhancement

via several pathways including direct modulation of the canonical learning and memory protein cascade and normalization of synaptic transmission in the hippocampus.

Alternative Targets

The AMPK agonist MFM is highly effective in normalizing insulin resistance in type 2 diabetes (Kirpichnikov et al., 2002; Knowler et al., 2002). It attenuates AD-like neuropathology in mouse models of diabetes by reducing hippocampal tau phosphorylation and one of the tau kinases, c-jun N-terminal kinase (Li et al., 2012), while also activating the tau phosphatase mTOR/protein phosphatase 2A in mouse primary neurons (Kickstein et al., 2010). MFM also ameliorates AD-like molecular and neuropathological hallmarks of insulin signaling in neuronal insulin resistance in the Neuro-2a cell line (Gupta et al., 2011). In addition, MFM reduces BACE1 and, as a consequence, A β production in SH-SY5Y-APP neuroblastoma cells, mouse primary cortical neurons, and wild-type mice (Hettich et al., 2014). Clinical studies reported conflicting results showing a reduced rate of onset of cognitive impairment (Dominguez et al., 2012) as well as a higher risk of developing AD (Imfeld et al., 2012). Hopefully the ongoing clinical trial (clinicaltrials.gov/ct2/show/NCT01965756?term=Alzheimer%27s+AND+metformin&rank=2) will clarify the therapeutic potential of MFM in AD, perhaps in a subset of patients with insulin resistance.

Several other therapeutic targets have also shown efficacy in animal models of AD. Other nuclear receptors (NRs) have shown interesting promise in AD partially due to the availability of high affinity, specific and selective ligands for retinoid $\times$ receptor, liver $\times$ receptors and PPAR δ (extensively reviewed in (Skerrett et al., 2014)), and emerging, next generation selective NR modulators (Marciano et al., 2014). While NRs can act on DNA response elements as either homodimers and/or heterodimers, a common partner for PPAR γ is the retinoid X receptor (RXR) which is activated by the agonist bexarotene, an exciting new therapeutic strategy in AD (Bomben et al., 2014) that targets ApoE to rapidly clear A β and reverse cognitive deficits in an animal model of AD although the involvement of insulin dysregulation in this paradigm remains undefined (Cramer et al., 2012; Mandrekar-Colucci and Landreth, 2011). Other approaches that don't directly target insulin but signal through pathways that converge on the insulin signaling axis (Yarchoan and Arnold, 2014) include the hormones glucagon-like peptide-1 (GLP-1), amylin, and leptin. GLP-1 prevented memory loss and neurodegeneration in APP/PS1 mice (McClean et al., 2011). The adipokine leptin is important in rodent spatial memory (Li et al., 2002) while amylin improved cognition in a LOAD mouse model (Adler et al., 2014). Finally, the mammalian target of rapamycin (mTOR), that acts via Akt and AMPK signaling, has shown significant promise in restoring cognitive function in several models of AD (Caccamo et al., 2014; Lin et al., 2013), though the mechanism of action is not yet known.

Alternative approaches

Lifestyle factors, described earlier, and environmental enrichment are other active areas of study to ameliorate cognitive decline (Polito et al., 2014) and reduce pathology (Lazarov et al., 2005) (Hu et al., 2010). Nonsteroidal anti-inflammatory drugs have been extensively tested in AD with mixed results (Gupta et al., 2014) as have several natural compounds including ginkgo biloba (Vellas et al., 2012), resveratrol (Kang et al., 2009), and cerebrolysin

(Rockenstein et al., 2006). With these varied approaches, it remains unclear whether any of these harness PPAR γ and/or ERK, or a subset of their respective signaling networks.

Disease stage-specific therapeutic windows?

The high glucose demand and insulin sensitivity of the brain confer an elevated propensity to insulin resistance with age and disease. This progression is illuminated by the observation that one month treatment with the insulin sensitizer RSG enhanced cognition in 9MO Tg2576 while neither 5MO nor 13MO Tg2576 responded to this treatment (Rodriguez-Rivera et al., 2011). In the same model, treatment from 8-13 MO provided cognitive protection (Escribano et al., 2009) indicating that in the absence of intervention, disease progression continues to a point where the therapeutic target is no longer appropriate.

In support of the therapeutic window concept, we found that suppression of calcineurin activity effectively reversed cognitive deficits in 5MO Tg2576 but not at older ages (Dineley et al., 2007). Interestingly, suppression of calcineurin activity improves insulin sensitivity in normoglycemic human subjects but exacerbates insulin resistance in diabetics (Ozbay et al., 2012; Porrini et al., 2008), supporting our observation that the therapeutic window for calcineurin intervention is in normoglycemic 5MO, but not older, insulin resistant Tg2576 (Figure 2). These observations may reveal the AD equivalent of the prediabetes state (De Felice and Ferreira, 2014) where elevated glucose, in the absence of overt insulin dyshomeostasis, can increase the risk of cognitive decline (Kerti et al., 2013). Similarly, the observation that 5MO Tg2576 have upregulated PPAR γ whereas it is downregulated in 9MO Tg2576 delineates the therapeutic window for intervention with PPAR γ agonism. Thus, we propose that disease stage-specific therapeutic windows exist for intervention, raising the possibility that other targets such as AMPK might be appropriate in more compromised cognitive performance. This hypothesis is further supported by defined AD stage-specific changes in neurogenic and glial markers (Ekonomou et al., 2014) as well as progression of the A β and tau oligomer profile (Dodge et al., 2014; Lasagna-Reeves et al., 2014). The age-dependent decline in Tg2576 hippocampal cognitive function, progression of insulin-related signaling dysfunction, and mechanistically distinct therapeutic interventions for enhancement of hippocampal cognition with advancing age, provides compelling evidence for disease stage-specific therapeutic windows.

Conclusions

Hippocampal memory failure is one of the earliest detectable traits of AD pathology (Boeve, 2012; Cavallucci et al., 2012). Therefore this review has focused on our understanding of the molecular processes of hippocampal learning and memory as it relates to early AD cognitive disruption. The importance of insulin resistance that accompanies type 2 diabetes and aging are significant risk factors for the looming epidemic of AD as our population ages. We purport that insulin signaling is a critical factor in brain homeostasis, metabolism, synaptic plasticity, and memory, imploring the need for therapeutic interventions that target the insulin signaling axis, in particular the common convergence point, ERK.

The data suggest that cognitive deficits in preclinical AD models are triggered by A β -mediated neuroinflammation and insulin resistance, mitochondrial dysfunction, and

impaired hippocampal ERK- dependent memory. We therefore postulate that progressive dysregulated hippocampal insulin signaling contributes to cognitive decline in some AD mouse models, and likely has clinical relevance for defining patient populations potentially responsive to mechanistically distinct insulin-sensitizer therapies. This perspective provides an important opportunity for appropriately designed stage-specific clinical trials in humans with early AD.

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Research Highlights

- Dysfunctional insulin signaling causes insulin resistance (IR) and perturbed metabolic function.
- IR is a risk factor for Alzheimer's disease (AD) cognitive decline.
- Animal models of AD have IR and cognitive decline similar to humans with AD.
- Insulin sensitizers improve IR and enhance cognition in animal models of AD.
- Animal models of AD reveal therapeutic windows of opportunity for cognitive enhancement.

Figure 1. Insulin signaling converges upon the ERK cascade

It is thought that A β -mediated neuroinflammation induces insulin resistance and hippocampal memory deficits since the insulin signaling axis couples to ERK. ERK is requisite for hippocampal memory consolidation and the insulin signaling axis converges on ERK via mediators of glucose utilization (GLUT, GSK-3 β), mitochondrial function (FOXO1), and energy metabolism (mTOR, AMPK). Insulin sensitizers target PPAR γ and AMPK to converge on ERK and memory consolidation through induction of CRE-containing genes. Many CRE-containing genes are also PPRE-containing genes indicating that PPAR γ may also participate in gene transcription-dependent memory consolidation.

Figure 2. Insulin resistance contributes to cognitive decline in Tg2576

Age-dependent exacerbation of insulin resistance manifested as sequential upregulation of calcineurin then down-regulation of PPAR γ (~9MO) and AMPK (~13MO) (lower panel dashed lines) suggest therapeutic windows for memory enhancement with mechanistically distinct insulin sensitizers to harness dysregulated ERK. While WT cognition declines slightly with age (solid grey line), by ~5MO Tg2576 exhibit significant deficits in hippocampus-dependent memory that require proper ERK function (solid black line). Coincident are significant pathologies for amyloid and tau that continue to worsen with age (dashed black line). Therapeutic windows have been identified by which to enhance cognition by sequentially targeting calcineurin, PPAR γ , and AMPK. FK = FK506.