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The role of insulin and neurotrophic factor signaling in brain aging and Alzheimer's Disease

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Abstract

Although increased lifespan is associated with reduced insulin signaling, insulin signaling is essential for neuronal development and survival. Insulin resistance is central to Type II diabetes and is also implicated in the pathogenesis of Alzheimer's Disease (AD). This has prompted ongoing clinical trials in AD patients to test the efficacy of improving insulin – like signaling with dietary ω-3 fatty acids or insulin – sensitizing drugs as well as exercise regimens. Here we review the role of insulin signaling in brain aging and AD, concluding that the signaling pathways downstream to neurotrophic and insulin signaling are defective and coincident with aberrant phosphorylation and translocation of key components, notably AKT and GSK3β, but also rac> PAK signaling. These responses are likely to contribute to defects in synaptic plasticity, learning and memory. Both oligomers of β-amyloid (which are elevated in the AD brain) and pro-inflammatory cytokines (which are elevated in the aged or AD brain) can be used to mimic the trophic factor/insulin resistance observed in AD, but details on other factors and mechanisms contributing to this resistance remain elusive. A better understanding of the precise mechanisms underlying alterations in the insulin/neurotrophic factor signal transduction pathways should aid the search for better AD therapeutic and prevention strategies.

Keywords: Insulin resistance; TZDs (thiazolidinediones); Brain aging

1. Introduction

Insulin signaling and longevity. Insulin signaling through insulin and insulin-like growth factors (IGFs) has evolved to represent the metabolic code which couples size and growth rates to the nutrient environment or food chain. Interspecies correlative data associate longevity with slow growth rates, large size, low predation and delayed reproduction, while shorter lifespans were associated with tumor promotion and mitogenic signaling for rapid growth for animals at the bottom of the food chain. Thus, in general, heavily predated smaller species that have adapted by R-selection for rapid growth and maturation have higher metabolic rates, fuel demands and shorter life spans than larger species closer to the top of the food chain that have evolved by K-selection for adaptation to the environmental carrying capacity. Insulin signaling appears integral to scale lifespan to the environmental niche. Thus, in recent years the familiar role of insulin in glucose regulation and diabetes has been extended beyond metabolism to mechanisms controlling aging rates, including caloric restriction. Consistent with the evolutionary perspective, insulin/IGF1 receptor signaling has been implicated as an important factor in invertebrate and vertebrate development, nutrient sensing, growth and aging (Hafen, 2004; Bartke, 2006). For example, scarce food and caloric restriction in the nematode *Caenorhabditis elegans* results in adaptive insulin signaling-dependent developmental arrest

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and long-lived dauer larvae. Genetic dissection of the dauer phenotype has identified a series of genes with mammalian homologues in the insulin signaling pathway (see below) that regulate invertebrate longevity beyond the dauer phenotype (e.g. *Daf-2*) (insulin/IGF-1 receptor), *Age-1 (PI3-K), Daf-16* (FOXO), *Daf-18* (PTEN), etc. Thus, partial loss of function in *Daf* genes leads to as much as a 3-fold increase in adult lifespan that is entirely dependent on *Daf-16* (FOXO), a regulator of the cellular stress response. Insulin pathway mutations also influence aging in mice where defects limiting signaling through IGF receptor 1 result in long-lived mice with increased resistance to oxidative stress (Holzenberger et al., 2004). It is easy to imagine that limited mitogenesis and slowed growth rates would also reduce tumor promotion. Further, because aging can be viewed as increased mortality from diminished resistance to physiological and cellular stress, insulin-like signaling, which plays an important role in the cellular stress response, would be suitably positioned to play a central role in governing aging rates.

While these and other data implicate increased insulin/IGF-1 signaling as a key *negative* regulator of lifespan, insulin/IGF-1 signaling also overlaps neurotrophin *survival* signaling that plays a significant *positive* role in the brain. This presents a small puzzle with seemingly opposing impacts. Our objective here is to explore the relationship of insulin-like signaling to pathology and diet that modulates insulin or trophic factor resistance and how this relationship impacts brain aging and Alzheimer's Disease risk.

2. Insulin signaling

The insulin receptor is a heterotetrameric tyrosine kinase receptor which, upon binding of insulin, undergoes dimerization and tyrosine autophosphorylation (see Fig. 1, readers unfamiliar with this literature may wish to refer to the GLOSSARY). Insulin binding activates the A subunit of the insulin receptor inducing a conformational change that leads to autophosphorylation of tyrosine residues in the B subunit; this allows recognition and further tyrosine phosphorylation of phosphotyrosine-binding (PTB) domains of adaptor proteins, for example, insulin receptor substrates (IRS) including IRS-1 and shc (reviewed Lizcano and Alessi (2002)). Different tyrosine phosphorylated IRS adaptor proteins then bind their effectors and transduce the insulin signal to multiple insulin response pathways. For example, IRS-1, SHC and Grb2 couple the insulin receptor to activate ERK/MAPK and downstream transcription factors (CREB and Elk-1) while, at least in insulin-sensitive peripheral tissues, IRS-2 and Cbl phosphorylation result in trafficking of the insulin-dependent glucose transporter, GLUT4, to the plasma membrane and increased glucose uptake. Insulin-receptor activation also creates phosphotyrosine containing binding sites for the Src homology 2 (SH2) domains of the p85 regulatory subunit of PI 3-kinase which results in catalytic p110 subunit phosphorylation of phosphatidylinositol (4,5) bisphosphate (PtdIns(4,5)P_2) and formation of the AKT activator, Ptd(3,4,5)P_3 (PIP3). AKT activation requires docking at the plasma membrane of AKT where it can be activated by phosphorylation at Thr 308 and ser 473 by kinases like protein kinase 3-phosphoinositide-dependent protein kinase-1 (PDK1). Plasma membrane docking involves PH domain binding to the PI3-K product PIP3 which is also accelerated by binding to phosphatidylserine (PS) and other acidic phospholipids on the inner leaflet of the plasma membrane. Fully active AKT is then released from plasma membrane to the cytoplasm by PTEN dephosphorylation of PIP3 at the D3 position of the inositol ring reverts the PI product back to PIP2. (Thus, PTEN puts the brakes on insulin signaling and acts as a tumor suppressor and PTEN mutations are second to p53 mutations as a cause of tumors.)

As the cascade continues, AKT then phosphorylates and inactivates both α and β cytosolic forms of glycogen synthase kinase 3 (GSK3), pro-apoptotic regulators, for example, BAD, and also modulates downstream TOR (Target of rapamycin) regulation of translation, and Nrf-2/ARE and FOXO/forkhead family member regulation of transcription.

3. Insulin signaling in the brain

Insulin is the prototypic trophic factor since trophic factor signaling overlaps the insulin pathways and is essential not only for neuronal development, but for continued survival *in vitro* and *in vivo*. In neurons, the ERK/MAPK and PI3-K> AKT> GSK3β, BAD, FOXO and TOR pathways are clearly critical for survival signaling, while regulation of glucose uptake is more problematic because in neurons it depends on GLUT3 rather than GLUT4. IGFs are potent neurotrophic agents (Carson et al., 1993) with increased expression after injury (Guthrie et al., 1995) that protect and rescue hippocampal neurons from amyloid and other toxins (Dore et al., 1997). IGF-1 can cross the blood brain barrier and is neuroprotective *in vivo* (Liu et al., 1995). Further, insulin-sensitizing agents such as troglitazones (thiazolidinediones, TZDs) can have potent neurotrophin-like survival activity (Nishijima et al., 2001). All of this contributes to the hypothesis that increased insulin-like signaling in the brain would promote neuronal survival and longevity.

4. Alzheimer's Disease (AD)

Alzheimer's Disease (AD), a devastating neurodegenerative condition associated with impaired memory and cognitive function, is affecting an estimated 4.5 million people in the United States, the majority of whom are over 65 years old, posing a great economic burden with an estimated cost of $42,000 per year per person (Rice et al., 1993). AD is characterized by two pathological hallmarks: senile plaques that are composed mainly of aggregated fibrillar insoluble β-amyloid (Aβ), and neurofibrillary tangles that include hyperphosphorylated tau protein, a microtubule-

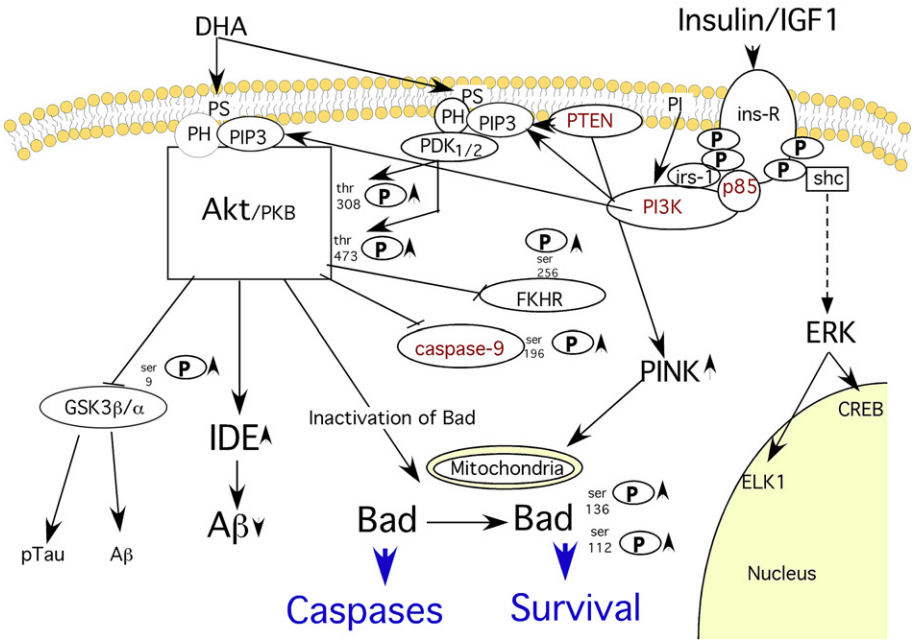

Fig. 1. DHA modulation of insulin and trophic factor signaling through AKT. Insulin/IGF1 and other neurotrophic factors act on receptors like the insulin receptor (ins-R) to induce cytoplasmic domain tyrosine phosphorylation (P) that permits coupling to adaptor proteins like shc which transduces the signal to the ERK/MAPK pathway leading to CREB and ELK1 transcription factors and to IRS-1 and the p85 subunit of PI3-K that transduce signals to AKT. PI3-K phosphorylates phosphatidylinositol (PI) to generate PIP-3 that along with phosphatidylserine (PS) permits docking of pleckstrin homology (PH) domain containing enzymes including PDK1/2 and its target Akt. The ω-3 fatty acid, DHA increases PS to upregulate docking and activation of Akt while PTEN induces neuroprotective PINK1 and dephosphorylates PIP3 to permit activated Akt to leave the membrane and activates important cytoplasmic and nuclear targets. These include GSK3, Bad, caspase 9 and the forkhead (FKHR) transcription factors. This insulin-like signaling restricts caspase activation which increases neuron survival, but also induces transthyretin and insulin degrading enzyme (IDE) that promote Aβ clearance while simultaneously inhibiting GSK3β, a major τ kinase. These are the pathways that likely impact AD pathogenesis.

binding protein important for physiological functions such as axonal transport and cellular communication (Ingelsson et al., 2004). At the cellular level, AD pathology is also associated with a state of neurite dystrophy characterized by fragmented neurites, neurite retreat and degeneration, postsynaptic protein loss and eventual neuronal death (Grace et al., 2002). Finally, at the molecular level, the neurodegenerative process involves activation of caspases (Newman et al., 2005) and probably calpain (Lee et al., 2000; Higuchi et al., 2005).

5. Insulin signaling and AD

5.1. Diabetes

Recent prospective and retrospective epidemiological findings indicate that type II diabetes mellitus is a significant risk factor for developing AD (Ott et al., 1996; Leibson et al., 1997; Ott et al., 1999). Type II diabetes mellitus, a metabolic disorder affecting approximately 5% of Americans, is characterized by insulin resistance, increased insulin secretion and overt hyperglycemia (Olson and Norris, 2004). The enhanced risk for developing AD in diabetic patients remains strong even when vascular factors are controlled, suggesting a non-vascular mechanism for AD pathogenesis (Peila et al., 2002). Several factors might contribute to the increased AD risk in diabetes mellitus, including defects in insulin signaling, accumulation of pathological Aβ and/or hyperphosphorylated τ.

5.2. Insulin and trophic factor levels in AD

The relationship between diabetes mellitus and AD is particularly intriguing given the finding that AD patients have lower CSF insulin levels and reduced insulin-mediated glucose disposal when compared to healthy control subjects (Craft et al., 1998, 2003). In the brain, insulin serves as a neuromodulatory and neuroendocrine molecule in addition to its usual metabolic function, playing a significant role in neuronal growth and survival (Gasparini and Xu, 2003). While there is very little insulin mRNA in the brain, recent ultra-sensitive PCR data show that insulin message can be detected in postmortem human brain and is reduced in the brains of Alzheimer Disease patients, leading the authors to suggest that Alzheimer's could be a "type III diabetes" due to loss of CNS insulin (Rivera et al., 2005; Steen et al., 2005).

In support of this novel hypothesis, the authors show that many insulin-sensitive endpoints are also reduced in AD brains. However, it remains to be demonstrated that the low level of insulin production in the brain is high enough to be functionally significant to neurons. Finally, knockout of the insulin receptor gene is not sufficient to cause cognitive deficits or neurodegeneration even though

some regions show enhanced GSK3β activity and τ hyperphosphorylation (Schubert et al., 2004).

The activity of many trophic factors is actually increased in AD brain (Uchida et al., 1988). One exception is BDNF (another neurotrophic factor), which shows large deficits in AD brain and plays a critical role in learning and memory (Connor et al., 1997) (reviewed in Pezet and Malcangio (2004)). Whether or not insulin itself is deficient in AD, there is substantial evidence for reduced insulin-like signaling that could be due to reductions in one or more neurotrophins or resistance to insulin and/or neurotrophins.

5.3. IGF-1

IGF-1 blocks amyloid toxicity by increasing survival signaling through ERK and PI3-K> AKT (Wei et al., 2002). Accordingly, increased activation of the insulin-like signaling pathway has been invoked to explain the limited neurotoxicity observed in APP transgenic mice accumulating high levels of β-amyloid from overexpressing APP. APP metabolites appear to induce IGF-2 increasing activated ERK and AKT and downstream phospho-Bad as well as transthyretin, an Aβ chaperone protein involved in Aβ clearance (Stein and Johnson, 2002). A subsequent study showed that selective immunoneutralization of transthyretin inhibits Aβ clearance and increases amyloid (Stein et al., 2004).

Insulin and insulin-like growth factor signal transduction sufficiently overlaps with neurotrophic factor signaling to effectively substitute for it *in vitro* (Aizenman and De Vellis, 1987). *In vivo*, insulin and insulin-like growth factor (IGF) signaling is strongly neuroprotective in a variety of models. For example, chronic subcutaneous infusion of IGF-1 has been reported to reduce CNS Aβ levels in aging rats and amyloid in the APPsw (Tg2576) transgenic mouse Alzheimer model (Carro et al., 2002). In that study, IGF-1 increased CNS transthyretin and albumin which were hypothesized to increase Aβ clearance. Further, additional experiments have shown that systemic IGF-1 can effectively treat older APPsw X PS1 mutant bigenic mice (Carro et al., 2005). And insulin signaling may have other ways to increase Aβ clearance.

5.4. Regulation of insulin degrading enzyme (IDE) and Aβ clearance

IDE not only plays a major role in insulin catabolism, but also mediates Aβ degradation (Farris et al., 2003). We have recently shown that insulin-mediated AKT activation is required for insulin-induced upregulation of IDE, a metalloprotease enzyme responsible for insulin degradation, presumably as a negative feedback control mechanism (Zhao et al., 2004). IDE has been observed in human CSF, and its activity, levels and mRNA are decreased in AD brain tissue (Cook et al., 2003). PI3-K> AKT mediated IDE upregulation as well as transthyretin induction raises the possibility of employing the insulin, BDNF or other neurotrophic signaling pathways as a strategy to increase transthyretin and IDE levels and Aβ clearance rates. Consistent with this hypothesis, a recent report by Ho et al., showed that insulin-resistance caused by high fat diet is associated with reduced IDE level, decreased PI3 kinase and AKT activation and increased amyloidosis in an APP transgenic AD animal model (Ho et al., 2004). There may also be an impact on Aβ production. AKT also inhibits GSK3α and an alternative explanation for the increased amyloid with insulin resistance (Ho et al., 2004) arises from data showing GSK3a stimulates generation of Aβ by γ-secretase (Phiel et al., 2003). The hypothesis that controlling insulin resistance is disease modifying has recently received some support from a study in the Tg2576 APPsw transgenic mouse model (Pedersen et al., 2006). The mice had high fasting glucose and glucocorticoids, and both metyrapone (inhibits corticosteroid synthesis) and rosiglitazone treatment reduced cognitive deficits and soluble Aβ, without reducing total amyloid accumulation.

However, insulin itself would be a poor treatment for many reasons. One is that insulin shares the same degrading enzyme with Aβ and thus competes with Aβ for IDE potentially reducing Aβ degradation (Vekrellis et al., 2000). In fact, acute insulin infusion causes an increased CSF Aβ42 level in subjects over 70 years of age (Watson et al., 2003) and plasma insulin levels are correlated with Aβ42 in minimally cognitively impaired subjects (Odetti et al., 2005).

While insulin is an unlikely therapeutic for AD, enhancing insulin-like signaling is another matter. In addition to inhibiting GSK3α and perhaps Aβ production and increasing Aβ clearance by increasing transthyretin and IDE, activated AKT may suppress the second AD pathological hallmark, hyperphosphorylated τ. AKT has been shown to be an upstream inhibitory kinase for GSK3β (ser9), a major τ kinase; thus GSK3β phosphorylation by AKT limits its ability to phosphorylate τ (Rickle et al., 2004). Therefore, stimulation of the neuroprotective BDNF or insulin signaling cascades, should protect against neuron loss and both amyloid and τ pathology, three significant hallmark AD lesions visible under the light microscope. But the clinical symptoms of AD are better correlated with synapse loss than these lesions.

5.5. Aβ oligomer-induced dendritic spine protein loss and PAK kinases

Ultimately, AD is a disorder of synaptic and cognitive deficits. Our laboratory and others have demonstrated that a number of postsynaptic markers enriched in excitatory neurons known to be involved in learning and memory are selectively lost in AD brain and AD animal models. One of the most vulnerable of these markers is an actin-binding protein, drebrin that is enriched in dendritic spines which protrude from dendrites as the postsynaptic sites for

pre-synaptic contact; structurally spines are entirely dependent on actin assembly (Calon et al., 2004, 2005). Consistent with spine loss seen on remaining pyramidal neurons using Golgi stains, remarkably large losses of drebrin, far exceeding estimates of neuron loss have been reported in AD hippocampus (Harigaya et al., 1996). Drebrin was first isolated from embryonic chicken brain as "developmentally regulated embryonic brain protein" (drebrin) (Shirao and Obata, 1985). It was later found to have actin-binding and regulatory activity, affecting the formation and stability of neuronal processes by modulating the formation of actin filaments and maintaining actin in a filamentous polymerized state (F-actin) (Hayashi et al., 1996). Anti-sense knockout of drebrin causes a defect in neurite outgrowth (Toda et al., 1999). As discussed below, insulin-like signaling can regulate drebrin and stabilize its association with actin via activation of AKT and regulation of peri-synaptic p21-activated kinases (PAKs) involved in actin assembly/disassembly in dendrites and spines. PAKs are serine/threonine protein kinases that serve as critical regulators of actin dynamics, primarily by inhibitory phosphorylation of LIMK1 which suppresses the actin-severing activity of downstream cofilin (Bokoch, 2003). PAKs play central roles in spine and synapse formation, stability, synaptic plasticity and learning and memory (Boda et al., 2004; Meng et al., 2005).

PAK involvement in AD arises because small soluble Aβ aggregates (oligomers) can suppress soluble PAK levels. In cultured neurons, Aβ oligomers induce fyn and focal adhesion kinases along with aberrant rac1-GTP activation within minutes of application (Chromy et al., 2003). This is coupled to activation and translocation of rac1's main downstream target, PAK, which translocates to membrane or particulate compartments, accompanied by a loss of active PAK in cytosol (Ma, Cole et al. submitted for publication). In the same study, chronic steady-state cytosolic PAK loss and translocation to membrane compartments were also found in AD and APPsw transgenic mice that produce high levels of Aβ. Aβ oligomers were implicated in drebrin and spine loss because direct application of oligomers to neurons *in vitro* caused a loss of inhibitory phosphorylation of cofilin resulting in its activation and a loss of drebrin's association with actin and reduced drebrin levels; further, *in vivo* anti-Aβ antibody infusion corrected cytosolic PAK and drebrin loss in APPsw transgenic mice (Zhao et al., 2006). A causal role for these PAK changes was inferred because transfection with kinase-active, wild type, but not kinase-dead mutant PAK protected primary neurons from oligomer-induced drebrin loss. One interpretation of these results was that aberrant oligomer-induced ectopic PAK signaling and cytosolic PAK deficits limit PAK availability and recruitment to appropriate signal transduction scaffolds for synaptogenic signaling, contributing to dendritic spine loss and cognitive decline. The large PAK defects found in AD may have an important cognitive impact because direct inhibition of PAKs using CNS infusion of a specific PAK inhibitor results in cognitive deficits in middle-aged animals (Zhao et al., 2006).

5.6. PAK and drebrin protection by insulin signaling

Consistent with PAK regulation by insulin-like signaling, PAKs have been found in a brain protein complex with PI3 kinase (Papakonstanti and Stournaras, 2002). This complex interacts physically with activated rac1-GTP (Kitamura et al., 1997). In support of the hypothesis that insulin-like signaling will modulate oligomer-induced defects in postsynaptic actin dynamics relevant to AD, insulin can protect from Aβ oligomer-induced drebrin loss *in vitro* (Zhao et al, unpublished). Several known mechanisms exist for insulin > AKT modulation of rac1-GTP > PAK signaling. AKT directly phosphorylates and limits activation of PAK's upstream activator rac1 at ser71 by suppressing rac1-GTP binding (Kwon et al., 2000). PAK translocation to focal adhesions (such as synapses) requires PAK binding in the region around PAK ser 21 with the adaptor protein, Nck. However, AKT phosphorylates PAK at serine 21 which disrupts Nck-PAK binding to adhesion sites permitting active PAK to recycle to cytosol (Zhou et al., 2003). Thus, AKT activation is theoretically able to mitigate aberrant Aβ oligomer-induced rac-GTP and downstream aberrant PAK translocation. In fact, AKT can also couple to PAK through ArgBP2γ and activate anti-apoptotic PAK survival signaling (Yuan et al., 2005). Downstream from PAK, LIMK1 phosphorylation of cofilin is an identified anti-apoptotic PAK signaling path (Yang et al., 2004, Chua et al., 2003). Thus, in addition to the classic ERK > CREB pathway, insulin or trophic factor signaling through AKT is a potentially important modulator of PAK dynamics that govern synaptogenesis, synaptic stability and plasticity.

5.7. Oxidative damage and inflammation

Aberrant Aβ aggregate induced rac activation is not only involved in aberrant PAK signaling, but likely plays an important role in inducing NADPH oxidase and related flavinoid proteins responsible for increased reactive oxygen species (ROS). For example, rac activation is implicated in NADPH oxidase production in reactive microglia (Hsu and Wen, 2002) and COX-2 induction (Wang et al., 2004). NADPH oxidase activity is aberrantly elevated in AD brain (Shimohama et al., 2000). Aβ induced rac activation is also likely involved in the rapid induction of an NADPH oxidase family enzyme in neurons that increases neuronal ROS production contributing to Aβ toxicity (Behl et al., 1994). Thus, insulin-like signaling and AKT's inhibitory phosphorylation of rac has potential to reduce ROS production and oxidative damage. Whatever the mechanism, insulin-sensitizing PPARγ agonists can limit amyloid-induced microglia activation and neurotoxicity (Combs et al., 2000).

5.8. Aberrant downstream insulin signaling in AD

PI3-Kinase activity is reduced in soluble, but not particulate compartments in AD brain suggesting a possible translocation (Jolles et al., 1992; Bothmer et al., 1994; Zubenko et al., 1999). Consistent with an aberrant activation and translocation event, phospho-ser473AKT was found to be increased in membrane/particulate fractions, but reduced in cytosolic fractions from AD brain (Griffin et al., 2005). While it is difficult to reliably evaluate phosphorylation patterns in postmortem AD and control brain, these alterations were confirmed by ICC and correlated with the progression of tangle pathology. Further, the redistribution of pAKT was accompanied by increased phosphorylation of AKT targets at relevant sites (pser9GSK3β, pser214τ, pser2448mTOR) in particulate fractions and a loss of nuclear staining. The authors observed a partial explanation for these changes in a loss and redistribution of PTEN (phosphatase and tensin homolog deleted on chromosome 10), the lipid phosphatase that dephosphorylates PIP3 thus releasing AKT from the membrane and permitting its migration to cytosol and nucleus. However, the status of PTEN remains unclear because in one subsequent report, no loss of PTEN in particulate, nuclear or total homogenates from AD temporal cortex was found (Rickle et al., 2006).

At first sight, the results showing AKT activation with inhibitory phosphorylation of GSK3β in AD seem inconsistent with the prevailing view that active GSK3 is increased in the cytosol of pre-tangle neurons and AD involves GSK3β activation leading to τ pathology resulting in large-scale efforts to develop specific GSK3 inhibitors to treat AD (reviewed in Bhat et al. (2004)). These apparently inconsistent results may be resolved by observations that increased active AKT and inactive GSK have been found in particulate fractions while reduced active AKT and active GSK have been found in cytosol. Specific increases in active dAKT in particulate fractions at the expense of other locations can be pathological, for example, in Drosophila lacking dPTEN, active particulate AKT has been shown to be the cause of embryonic lethal effects (Stocker et al., 2002). One explanation is that there are important cytosolic and nuclear substrates for the PI3-K > AKT pathway that include not only GSK3 and τ, but also the caspase regulator, Bad, the transcription factor FOXO and the antioxidant defense system regulator, Nrf-2 (Lee and Johnson, 2004). In particular, PI3-K > AKT induction of Nrf-2 > ARE signaling mediates upregulation of the glial and neuronal expression of Phase II enzymes and antioxidant defenses including FOXO3a (Li et al., 2004). Conversely, Nrf2 null mice showed reduced FOXO3a expression (Hu et al., 2006). Thus, while AKT phosphorylation of FOXO is expected to reduce access to the nucleus and antioxidant defense enzyme production, AKT phosphorylation of Nrf-2 in the cytosol has an opposing pro-survival effect by increasing ARE-mediated transcription of defense enzymes and levels of FOXO3a. The literature shows an overall protective effect of insulin and neurotrophic signaling in neurons.

5.9. Insulin resistance and AD

An emerging body of evidence supports the hypothesis that Alzheimer's Disease involves not so much a loss of insulin and other trophic factors, but a resistance to them (Watson and Craft, 2003).

6. Possible causes of insulin resistance relevant to AD

6.1. Amyloid peptides

Aβ aggregates can activate τ kinase 1 (GSK3β) (Takashima et al., 1993), an activity shared by Aβ oligomers which activate GSK3β *in vitro* and *in vivo* (Ma et al., 2006). GSK3β has many substrates, including IRS-1 which results in impaired insulin signaling (Eldar-Finkelman and Krebs, 1997). More recently, several groups have shown that pre-exposure of cultured neurons to soluble Aβ aggregates (oligomers) impairs the ERK response to NGF (Chromy et al., 2003) and the response to BDNF (Tong et al., 2004). In the latter study, sublethal doses of soluble Aβ aggregates (including oligomers) suppressed BDNF induced ERK > CREB/Elk-1 and PI3-K > AKT signaling downstream of TrkB, apparently at the level of IRS-1 and Shc tyrosine phosphorylation. These data in primary neuron cultures support a direct Aβ induction of trophic factor resistance beyond the specific receptor level. However, there may also be indirect mechanisms.

6.2. Inflammation

AD and aging are both associated with low level chronic inflammation associated with increased pro-inflammatory cytokines including IL-1β and TNFα that are known to signal through AP-1 and NFKB (Akiyama et al., 2000). TNFα, for example is well-known to induce insulin-resistance in peripheral tissues, apparently at the level of reducing IRS-1 tyrosine phosphorylation, an effect that can be blocking by insulin sensitizing thiazolidinediones (TZDs) typically used to treat type II diabetes (Peraldi et al., 1997). In support of this mechanism, serum TNFα levels are increased and correlate negatively with free IGF-I in Alzheimer Disease (Alvarez et al., 2006). CNS TNFα increases with brain aging and antagonizes IGF-1 induced increases in Aβ clearance (Carro et al., 2002). Consistent with inflammatory cytokine-mediated insulin resistance in the brain, increases in pro-inflammatory cytokines like IL-1β in aging rat cortex have been associated with reduced insulin-like signaling (MAPK and PI3-K > AKT pathways) in the absence of deficits in NGF or BDNF (Maher et al., 2004). These changes could be mitigated by another insulin-sensitizing approach, the dietary ω-3 fatty acid, eicosopentaenoic acid (EPA).

6.3. Obesity, Type II diabetes and brain aging

High saturated fat diets (Morris et al., 2003), obesity and type II diabetes (Ott et al., 1996, 1999) have been associated with increased risk for dementia, including AD. In general obesity is associated with a "metabolic syndrome", pro-inflammatory cytokine elevation and insulin resistance. Consistent with insulin resistance, Craft and colleagues found that AD patients have higher plasma fasting insulin than controls but lower CSF insulin and CSF/plasma insulin ratios. Surprisingly, patients who were homozygous for apolipoprotein E4 (apoE4), a major genetic risk factor for AD, tended to have normal insulin levels (Craft et al., 1998).

One modifiable influence that may promote cognitive deficits is the typical Western diet which is high in saturated and trans fats and low in ω-3 fatty acids. ω-3 fatty acid deficiency is prevalent in the US and a recent RAND meta-analysis of available data suggests data is already strong enough to warrant clinical trials (Maclean et al., 2005a). High fat diets are known to reduce insulin signaling and, in animal studies to reduce hippocampal levels of BDNF, a potent neurotrophic factor involved in learning and memory that also stimulates PI3-K>AKT signaling (Pezet and Malcangio, 2004; Tong et al., 2004). Insulin resistance from a high fat diabetogenic diet, increases amyloid production and deposition in APP transgenic mice (Ho et al., 2004). Conversely, high ω-3 fatty acid diets which are known to mitigate insulin resistance (Delarue et al., 2004), also reduce amyloid production and deposition in APP transgenics (Lim et al., 2005). As discussed above, insulin/IGF-1 signaling may inhibit Aβ production and also induce both the Aβ degrading enzyme IDE and transthyretin, an Aβ chaperone that promotes clearance. In fact, ω-3 rich fish oil has been shown to induce hippocampal transthyretin in aging rat brain (Puskas et al., 2003). The fish oil enriched ω-3 fatty acid DHA has also been shown to reduce Aβ production and to be strongly neuroprotective in primary human neuron cultures (Lukiw et al., 2005). These effects appear to be due a recently discovered lipoxygenase-derived DHA metabolite named neuroprotectin D1 (NPD1). Whatever the mechanism, our group and others have repeated observations of DHA or fish oil mediated amyloid reductions in transgenic mouse models.

7. Clinical approaches

7.1. Insulin

Acute treatment with a bolus of glucose known to stimulate insulin release (Craft et al., 1992) or insulin at 85 microU/ml can increase memory in AD patients. Craft and colleagues performed a dose-response trial with acute insulin treatment (with glucose clamped) on memory in AD patients and normal volunteers (Craft et al., 2003). Results again showed improved memory in non-ApoE4 AD patients at higher insulin doses (35 and 85 microU/ml), but improvements in ApoE4 patients only at lower doses (25 microU/ml). The authors concluded that the non-ApoE4 patients were comparatively insulin-resistant, consistent with earlier data showing they had higher insulin levels. Conversely, the same group has found that ApoE4 patients have reduced insulin-degrading enzyme (Cook et al., 2003).

7.2. Insulin-sensitizers – TZDs

TZDs are peroxisome proliferating activating receptor γ (PPAR-γ) agonists that are used clinically to sensitize insulin receptors and also possess anti-inflammatory activity. They can prevent insulin resistance induced by pro-inflammatory cytokines (Peraldi et al., 1997) which makes them reasonable candidates for treating deficits in AD. In neuronal cultures, TZDs can suppress amyloid induced pro-inflammatory cytokine production and neurotoxicity (Combs et al., 2000) and under inflammatory conditions, they can limit BACE1 expression (Sastre et al., 2003) and to a limited extent amyloid accumulation in APP transgenics (Yan et al., 2003). Given the animal data and the evidence that Type II or insulin-resistant diabetes increased AD risk and that treatment with insulin could improve cognitive function in AD patients, Craft and colleagues performed a preliminary 6 month clinical trial with 20 AD patients receiving an insulin-sensitizing TZD, rosiglitazone and 10 patients on placebo and found evidence for slowed cognitive decline (Watson et al., 2005). This has now been followed by a larger rosiglitazone trial with treatment-related slowing of disease progression in non-ApoE4 patients (Risner et al., 2006).

7.3. Exercise

Like diet, exercise is one of the classical tools to fight obesity, metabolic syndrome and associated insulin resistance. Exercise induces functionally neuroprotective increases in brain derived neurotrophic factor (BDNF) (Neeper et al., 1995). Unlike NGF, another major CNS trophic factor, BDNF, actually does show deficits in AD (Connor et al., 1997; Pezet and Malcangio, 2004) and has target neurons that are vulnerable in AD hippocampus where neurons actually die back or are lost. Increased exercise has been associated with reduced AD risk (Larson et al., 2006). In addition, exercise increases systemic IGF-1 (Schwartz et al., 1996) which, as cited above, crosses the blood brain barrier and promotes amyloid clearance. Exercise in the context of "environmental enrichment" has recently been shown to promote amyloid clearance in a transgenic model (Lazarov et al., 2005). In general, the exercise and lifestyle changes devised to control cardiovascular disease (CVD) risk show promise in preventing AD since AD and CVD share many of the same risk factors. Finally, exercise may even prove useful in treating AD (Stevens and Killeen, 2006).

7.4. ω-3 (n − 3) fatty acids

ω-3 fatty acids are well-known insulin-sensitizing agents in peripheral tissues (Taouis et al., 2002) and increased ω-3 consumption is associated with not only reduced cardiovascular disease, but reduced AD risk (reviewed in (Maclean et al., 2005b)). The ω-3 fatty acid, docosahexaenoic acid (DHA) has at least 2 neuroprotective mechanisms. It facilitates AKT activation and survival signaling by increasing membrane phosphatidylserine which participates in pleckstrin homology domain docking with PIP3 at the plasma membrane (Akbar et al., 2005). DHA is also the precursor of a neuroprotective lipid signaling molecule call neuroprotectin D1 (NPD1) that is markedly reduced in AD hippocampus and a potent modulator of apoptotic regulatory proteins, including BAD, Bcl2, BAX, etc (Lukiw et al., 2005). Both pathways may protect against synaptic marker loss in AD. DHA administration reduced caspase activation and the loss of molecules involved in postsynaptic plasticity (PSD-95 and drebrin) and memory loss in a AD transgenic model mice on a DHA-depleting high safflower oil diet (Calon et al., 2004). Finally, DHA protects against Aβ oligomer neurotoxicity *in vitro* (Florent et al., 2006).

7.5. Small molecule insulin and trophic factor mimetics

Insulin possesses potential tumor promoting mitogenic activity and shares the same degrading enzyme with Aβ and thus competes with Aβ for IDE potentially reducing Aβ degradation (Vekrellis et al., 2000). This latter concern is justified by a recent study which revealed that insulin infusion causes an increased CSF Aβ42 level in subjects over 70 years of age (Watson et al., 2003). Therefore, a small molecule insulin mimetic, demethylasterriquinone B1 (DAQ B1), that does not competitively inhibit IDE, is an alternative approach. DAQ B1, synthesized by Merck Research Laboratory in 2001, was found to be an orally active insulin receptor modulator lacking mitogen-related adverse side-effects (Salituro et al., 2001). It induces PI3 kinase and AKT activation as well as insulin, and is functional in that it reduces glucose levels in diabetic patients and induces a subset of the gene expression changes produced by insulin, but not those involved in proliferation (Webster et al., 2003). Another advantage of DAQ B1 over insulin is its hydrophobicity, which would allow it to pass blood brain barrier, a prerequisite for a successful CNS drug. DAQ B1, therefore, is a candidate molecule to be used as an intervention for AD acting like insulin at the levels of τ and Aβ pathology as well as synaptic drebrin-actin dysfunction. Our lab is currently exploring the efficacy of DAQB1 in models for Alzheimer pathogenesis.

7.6. Conclusion

While reduced insulin-like signaling can promote longevity, the same pathways are critical for neuronal survival and plasticity that underlies memory and learning. Data collected from cell culture, animal models and limited human tissue suggest that age-related inflammation or increased production of amyloid peptides in AD may cause insulin and neurotophic factor resistance that can contribute to increases in amyloid peptides via a positive feedback loop. These data also suggest that the brains of AD patients have dysregulated insulin-like signaling. While additional research is needed to understand the mechanisms involved in the dysregulated insulin and trophic factor signaling and to develop better treatments, clinical trials have already begun using insulin-sensitizing drugs, exercise regimens and dietary inclusion of ω-3 fatty acids.

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Glossary and Abbreviations

Aβ: Amyloid β-protein. 40–42 amino acid self-aggregating peptide implicated in AD

AD: Alzheimer's disease. Age-related dementing disease with plaques and tangles

AKT: Protein kinase B (after AKT oncogene). Major "pro-survival" kinase

AP-1: Activator protein-1. A transcription factor

ApoE: Apolipoprotein E. Lipoprotein involved in cholesterol and Aβ transport. Allelic variant, ApoE4, is the major genetic risk factor for AD.

APP: Amyloid β-protein precursor, releases Aβ after cleavage by proteases (secretases)

APPsw: APP with "Swedish" mutation, increases Aβ production

ARE: Antioxidant response element, transcription factor regulating defense enzymes

BACE1: β-secretase, cuts APP at N-terminus of Aβ

BDNF: Brain-derived neurotrophic factor, a major trophic factor related to learning

Cofilin: An actin filament severing protein that is inhibited by PAK to LIMK1

COX-2: Cyclooxygenase 2, inducible enzyme target of anti-inflammatory drugs

CREB: cAmp response element binding protein, transcription factor related to learning

CSF: Cerebrospinal fluid, bathes brain

CVD: Cardiovascular disease

DAQB1: Dimetheylasterriquinone B1, an insulin mimetic small molecule

DHA: Docosahexaenoic acid (C22:6 $\boldsymbol{n-3}$)

Elk-1: An insulin-regulated transcription factor

ERK: Extracellular regulated kinase, involved in mitogenesis, memory and survival

FOXO: Forkhead, box transcription factor class O (mammalian homologue of Daf16)

GLUT4: Glucose transporter 4, central to peripheral insulin-dependent glucose uptake GLUT3. glucose transporter 3, major regulator of neuronal glucose uptake

Grb2: An SH2 adaptor protein that couples activated receptor to ERK/MAPK

GSK3α/β: Glycogen synthase kinase 3 (α/β) has many substrates, including τ

IDE: Insulin degrading enzyme, also major Aβ-degrading enzyme

IGF: Insulin-like growth factor, for brain, notably IGF-1

IL-1β: Interleukin 1β (pro-inflammatory cytokine)

IRS-1/2: Insulin receptor substrate 1/2 (adaptor protein) coupling receptor to PI3-K
LIMK1: LIM kinase 1, provides inhibitory control over cofilin, an actin-severing protein
MAPK: Mitogen activated protein kinase (e.g., ERK1, ERK2)
NGF: Nerve growth factor, important for cholinergic neuron survival in brain
NPD1: Neuroprotectin D1, a neuroprotective enzymatic product of DHA
Nrf-2: NF-E2 related factor 2, an ARE regulating transcription factor
P85: Regulatory subunit of PI3-kinase, transduces insulin signals to AKT pathway
P110: Catalytic subunit of PI3-kinase
PAK: p21-activated kinase family (PAK1,2,3, 4, 5) b regulates actin through LIMK1
PDK1: Phosphoinositide-dependent protein kinase 1, activates docked AKT
PH: Domain pleckstrin homology domain, required for AKT plasma membrane docking
PI3-K: Phosphatidylinositol 3 kinase, a major survival kinase upstream of AKT
PPARγ: Peroxisome proliferating activating receptor γ, target of TZDs
PINK1: PTEN induced kinase 1, a neuroprotective kinase
PIP3: Phosphatidylinositol 3,4,5 (phosphate)3, PI3-K product that docks ATK
PTEN: Phosphatase and tensin homolog deleted on chromosome 10, regulates AKT
PS: Phosphatidylserine, promotes AKT membrane docking, regulated by DHA
PS1: Presenilin 1, γ-secretase complex component cutting APP at Aβ C-terminus
Rac1: Small G protein activator, involved in Aβ oligomer activation of PAK
ROS: Reactive oxygen species (e.g., superoxide, singlet oxygen, hydroxyl free radicals)
SH2: src homology domain 2, adaptor proteins use to couple to signaling pathway
SHC: An SH2 adaptor protein that couples insulin signaling to ERK/MAPK
TNFα: Tumor necrosis factor α, (pro-inflammatory cytokine)
TOR: Target of rapamycin, AKT target that regulates FOXO/forkhead
TrkB: High affinity neurotrophin receptor component involved in survival signaling
TZDS: Thiazolidinediones, PPAR ligands used to treat insulin-resistance