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Hippocampal calcium dysregulation at the nexus of diabetes and brain aging

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Abstract

Accumulating evidence is associating disorders of lipid and glucose metabolism, including the overlapping conditions of insulin resistance/metabolic syndrome, obesity and diabetes, with moderate cognitive impairment in normal aging and elevated risk of Alzheimer's disease. It appears that a common feature of these conditions is deficient insulin signaling, likely affecting the brain as well as canonical peripheral target tissues. A number of studies have documented that insulin directly affects brain processes and that reduced insulin signaling results in impaired learning and memory. Several studies have also shown that deficient insulin signaling induces Ca^{2+} dysregulation in neurons. Because brain aging is associated with substantial Ca^{2+} dyshomeostasis, it has been proposed that deficient insulin signaling exacerbates or accelerates aging-related Ca^{2+} dyshomeostasis. However, there have been few studies examining insulin interactions with Ca^{2+} regulation in aging animals. We have been testing predictions of the Ca^{2+} dysregulation/diabetes/brain aging hypothesis and have found that insulin and insulin sensitizers (thiazolidinediones) target several hippocampal Ca^{2+} -related processes affected by aging, including larger Ca^{2+} transients and Ca^{2+} -dependent afterhyperpolarizations, and counteract the effects of aging on those processes. Thus, while additional testing is needed, the results to date are consistent with the view that effects of deficient insulin signaling on brain aging are mediated in part by neuronal Ca^{2+} dyshomeostasis.

Keywords

afterhyperpolarization; thiazolidinediones; cognition; imaging; aging; learning

1.0 Introduction

Metabolic syndrome is generally defined as a constellation of symptoms consisting of insulin resistance, compensatory hyperinsulinemia, dyslipidemia, hypertension, and central obesity. As insulin secretion begins to fail, the syndrome frequently converts to Type 2 diabetes mellitus (T2DM) and hyperglycemia. Metabolic syndrome/diabetes is a major risk factor for cardiovascular disease and its prevalence is increasing dramatically worldwide (Reaven, 2005). The syndrome and/or diabetes can result from a sedentary lifestyle, an atherogenic diet, and/or obesity. Notably, the steady rise in obesity of recent years is

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predicted to offset gains made in life expectancy during the last two centuries (Olshansky et al., 2005). Individuals with insulin resistance at mid-life have a considerably shorter life span (reviewed in Curtis et al., 2005; Facchini et al., 2001) whereas, interestingly, centenarians have a very low incidence of insulin resistance and diabetes (Baranowska et al., 2006; Barbieri et al., 2001; Takayama et al., 2007).

In addition, metabolic syndrome/ diabetes is increasingly recognized as a major risk factor for aging-related cognitive dysfunction or Alzheimer's disease (AD) (Craft, 2007; de la Monte, 2012; Fishel et al., 2005; Gustafson, 2006; Rivera et al., 2005; Whitmer et al., 2007; Yaffe et al., 2004; Yaffe et al., 2012). Several components of the syndrome have been linked to altered brain functions. In particular, insulin resistance seems of interest in this regard because insulin exerts clear effects on brain functions relevant to AD, including increased beta amyloid clearance and improved cognitive performance (Craft, 2006; 2007; Fishel et al., 2005). Moreover, diabetes and insulin resistance are associated with neuronal Ca^{2+} dysregulation (Biessels et al., 2002a; Verkhratsky and Fernyhough, 2008) and impaired brain synaptic plasticity (Gispén and Biessels, 2000; Stranahan et al., 2008c; Zhao and Alkon, 2001). Further, glucocorticoids, which likely contribute to peripheral insulin resistance (Pedersen et al., 2006; Seckl and Walker, 2004), also play a role in brain aging and cognitive impairment (Bizon et al., 2009; Issa et al., 1990; Landfield et al., 1981; Landfield et al., 2007; Lupien et al., 1998; McEwen et al., 1999; Piroli et al., 2007; Sapolsky, 1999; Seckl and Walker, 2004; Stranahan et al., 2008b). Despite these intriguing connections, however, the underlying mechanisms by which metabolic syndrome/diabetes affects cognitive function are still not clear.

2.0 Metabolic Syndrome/Diabetes as a Risk Factor for Cognitive Impairment

2.1 Obesity, metabolic syndrome and cognitive dysfunction

A Western diet rich in fat and calories in combination with a sedentary life style is known to increase visceral fat mass and circulating free fatty acids (FFAs). It is believed that this increase in FFAs, in turn, causes an increase in adipokine release from adipose tissue (e.g., TNF- α), ultimately resulting in widespread tissue inflammation (Perseghin et al., 2003; Reaven, 1988; Weisberg et al., 2003; Xu et al., 2003). FFA-mediated inhibition of the insulin receptor signaling pathway is also recognized as a likely pathway linking obesity to insulin resistance in target tissues (mostly liver, muscle and fat). Several reports indicate that elevated plasma FFAs induce insulin resistance through inhibition of glucose transport, mediated, in part, by a decrease in phosphatidylinositol 3-kinase (PI3K) and its interaction with insulin receptor substrate 1 (IRS1) (reviewed in Curtis et al., 2005; Dresner et al., 1999; Furuhashi et al., 2007; Griffin et al., 1999; Itani et al., 2002; Kim et al., 2001; Yu et al., 2002). Further support for a connection between obesity and diabetes comes from experiments in which removal of visceral fat prevents insulin resistance in animal models (Barzilai and Rossetti, 1995; Gabriely et al., 2002), (although preliminary studies indicate that removing visceral fat in humans does not resolve symptoms of diabetes (Klein, 2010)). In addition, numerous rodent studies have shown high fat diets can induce specific aspects of metabolic dysfunction, including decreased insulin sensitivity, elevated cholesterol levels and increased body weight (Axen et al., 2003; Barnard et al., 1998; Keenan et al., 2005; Mielke et al., 2006; Petro et al., 2004; Storlien et al., 1986). Conversely, it is also recognized that chronic caloric restriction is capable of decreasing insulin resistance and reducing biomarkers of aging (Austad, 1995; Ingram et al., 2004; Keenan et al., 1995; Lim et al., 2011; reviewed in Martin et al., 2006; Mattson, 2000).

In humans, a body mass index (BMI) >30 at midlife is associated with increased risk of dementia (Whitmer et al., 2007). A recently published 30 year longitudinal study with $>6,000$ participants specifically looked at the relationship between abdominal fat and risk for

developing dementia later in life (Whitmer et al., 2008). Dementia was approximately three times higher in those with the greatest, compared to the group with the lowest, abdominal diameters. Given the increased incidence of obesity in adults, these studies highlight the need for identifying the mechanisms underlying the association of central/visceral obesity and dementia.

2.2 Deficient insulin signaling and cognitive decline

Results from over two decades of research have shown that impaired glucose tolerance and T2DM, can negatively impact brain function. Depending on the severity and the duration of the disease, as well as on the age of the individual, the condition is associated with varying degrees of cognitive and memory deficits, attention deficits, slower processing speeds, motor dysfunction, and depression (Ryan, 1988; Tun et al., 1990; Gradman et al., 1993; Biessels et al., 1994; Croxson and Jagger, 1995; Kalmijn et al., 1995; Gregg et al., 2000; Ryan and Geckle, 2000; Zhao and Alkon, 2001; Reagan, 2002; Awad et al., 2004; Messier, 2005; Munshi et al., 2006). A recent meta-analysis shows that there is a strong positive correlation with diabetes progression and the onset of AD (Biessels et al., 2006; Luchsinger et al., 2011) and it has been suggested that AD might represent a CNS specific state of diabetes termed “Type 3 diabetes” (de la Monte et al., 2006; Gasparini et al., 2002; Lannert and Hoyer, 1998; Steen et al., 2005). While there is considerable evidence that insulin resistance associated with T2DM may be an important pathogenic factor in both normal aging and AD (Biessels et al., 2006; Craft et al., 2012; Watson and Craft, 2003), recent studies show that under some circumstances, insulin resistance may be associated with slower decline (Burns et al., 2012). Generally, however, higher plasma insulin but lower brain insulin levels are correlated with a decline in cognitive status (Cole and Frautschy, 2007; Craft et al., 1998; Janson et al., 2004; Ott et al., 1999; Steen et al., 2005; Watson and Craft, 2004) suggesting that a potential mechanism underlying the effect in the brain may be down-regulation of insulin and glucose transporters at the blood brain barrier (Baura et al., 1996; Craft, 2005; Duelli et al., 2000; Korol and Gold, 1998; McNay, 2005; Simpson et al., 1999). Similarly, reduced brain glucose metabolism (PET imaging) correlates well with mild cognitive impairment and AD (de Leon et al., 2007; Eberling et al., 1995; Mosconi et al., 2004; Swerdlow, 2007). It should be noted, however, that brain insulin resistance in AD has been reported in the absence of diabetes (Talbot et al., 2012). Taken together, the results appear to provide strong evidence that impaired insulin signaling in the brain is associated with unhealthy brain aging and higher risk for conversion to AD.

Multiple mechanisms have been proposed to mediate the association of age-related cognitive decline and diabetes, including decreased ATP production, poor A β clearance or degradation, weak synaptic communication, hyperphosphorylation of microtubule-associated proteins (Tau), altered Ca²⁺ regulation, elevated glucocorticoids and increased 11 β hydroxysteroid dehydrogenase activity (Awad et al., 2004; Benedict et al., 2007; Biessels et al., 2008; Biessels et al., 2006; Craft and Watson, 2004; Gasparini et al., 2002; Korol and Gold, 1998; Kulstad et al., 2006; Messier et al., 2003; Ott et al., 1999; Reagan, 2002; Reger et al., 2008; Ryan and Geckle, 2000; Seckl and Walker, 2004; Stranahan et al., 2008a; To et al., 2011; Yaffe et al., 2004; Zhao et al., 1999). However, because of the complexity of interacting factors and likely contributions from multiple processes, it remains unclear which diabetes-related mechanisms may be linked to cognitive decline and onset of AD.

3.0 Effects of insulin on brain processes

3.1 Insulin modulation of neuronal activity

It has been recognized for some time that acute insulin exposure can directly alter brain neuronal activity, and that insulin treatment of hippocampal slices inhibits firing of pyramidal neurons (Palovcik et al., 1984). Since then, insulin receptors have been identified in the hippocampus (Folli et al., 1996; Zhao et al., 1999) and shown to participate in both developmental and brain aging processes (see van der Heide et al., 2006). Insulin also enhances activity of Ca^{2+} -dependent large-conductance K^+ channels (O'Malley et al., 2003), results that are consistent with the inhibition of neuronal firing by acute insulin (Palovcik et al., 1984). Also consistent with this inhibitory effect is evidence that a tonic GABA current is activated within one hour of insulin application to hippocampal slices (Jin et al., 2011).

Other evidence shows, however, that insulin also modifies synaptic plasticity and lowers threshold frequencies for eliciting LTP and LTD (van der Heide et al., 2005). Insulin increases delivery of NMDA receptors to the membrane and potentiates NMDA-evoked currents (Skeberdis et al., 2001), which could, in part, be responsible for the effects on synaptic plasticity. Further, aging female mice that manifest learning deficits are characterized by impaired mitochondrial function and altered brain glucose metabolism (Brinton, 2008; Simpkins et al., 2012; Yao et al., 2010). Similarly, we have found that aged male rats impaired in learning the Morris water maze (MWM) task exhibit decreased hippocampal expression of genes related to insulin signaling and mitochondrial function (Rowe et al., 2007). On the other hand, expression of brain insulin receptors is increased by learning paradigms, suggesting importance for memory processing (Zhao et al., 1999).

A few studies have also examined the effects on learning of direct insulin treatment of the brain in animal models. In one study, a single intracerebral insulin injection, enhanced performance in rats on a passive avoidance task 24h later (Park et al., 2000). Interestingly, however, prolonged (3 month) intracerebral insulin infusion had negative consequences on hippocampal physiology related to learning and memory, elevating several Ca^{2+} -mediated processes, including the slow afterhyperpolarization (sAHP) (Kamal et al., 2012). These results suggest that there are major differences in the effects of short- vs long-term insulin exposure and are consistent with the possibility that long-term exposure to elevated insulin is a key factor in the induction of brain insulin resistance. However, it is also likely that insulin dosage and other factors, including gender, are important in determining the consequences of insulin exposure.

3.2 Insulin-Sensitizing Agents (PPAR- γ Agonists) and Improved Brain Function

The thiazolidinediones (TZD), rosiglitazone and pioglitazone, are 2nd generation peroxisome proliferator-activated receptor (PPAR)- agonists used to treat T2DM and are “insulin sensitizing” agents. A genome-wide association study confirmed that the gene for PPAR- is a risk factor for Type 2 diabetes, further identifying these nuclear receptors as important therapeutic targets (Scott et al., 2007). Evidence indicates that rosiglitazone significantly improves cognition and verbal memory in AD patients with mild cognitive impairment (Kulstad et al., 2004; Watson et al., 2005). Additionally, AD patients lacking the ApoE4 allele appear to be selectively sensitive to the beneficial effects of chronic treatment with rosiglitazone (Risner et al., 2006). In patients with T2DM, tighter glycemic control achieved by adding rosiglitazone to existing therapy, resulted in improved working memory (Ryan et al., 2006). Several mechanisms have been proposed by which TZDs exert cognition-preserving and neuroprotective effects, including lowering insulin resistance, glucose and cholesterol levels as well as decreasing inflammation, dyslipidemia and A load (Cholerton et al., 2011; Sundararajan et al., 2006). Together, these results in humans along

with others in animals (Gemma et al., 2004; Pedersen et al., 2006) provide strong evidence consistent with the view that improved insulin signaling may preserve or improve cognitive function in aging.

3.3 Streptozotocin (STZ)-Induced Diabetes

Experimentally-induced diabetes is commonly studied in animal models using peripheral injections of STZ, which induce hyperglycemia via destruction of insulin-producing pancreatic beta cells. Most studies of STZ-treated animals find impairment of hippocampal-dependent learning tasks (e.g., MWM, active avoidance, and object recognition) when insulin deficiency and hyperglycemia are induced in young-adult animals (Baydas et al., 2003; Biessels et al., 1996; Biessels et al., 1998; Dou et al., 2005; Kamal et al., 2000; Popovic et al., 2001). This model is also associated with dendritic retraction, loss of synaptic contacts (Magarinos and McEwen, 2000) and alterations in NMDARs (Gardoni et al., 2002; Li and Wei, 2001). In aging animals, STZ-induced diabetes accelerates age-dependent decline of behavioral (MWM) and synaptic (LTP) plasticity (Kamal et al., 2000).

Another type of STZ model is generated by direct injections of STZ into the brain. While such CNS injections do not result in loss of insulin-producing pancreatic beta cells or peripheral hyperglycemia, they reduce expression of genes related to insulin signaling in the brain (Duelli et al., 1994; Lester-Coll et al., 2006). STZ injection directly into the brain causes cell loss accompanied by increases in Tau and A β immunoreactivity, and has been suggested as a model of sporadic AD (Duelli et al., 1994; Grunblatt et al., 2007; Lester-Coll et al., 2006; Plaschke et al., 2010). Intracerebral STZ, results in progressive impairment over the course of a few weeks on several memory tasks, including the hole-board test, passive avoidance, MWM, and elevated plus maze (Agrawal et al., 2011; Lannert and Hoyer, 1998; Nitsch and Hoyer, 1991; Pathan et al., 2006; Sharma and Gupta, 2001). Thus, although peripheral and CNS STZ models do not recapitulate the insulin resistance commonly seen in human aging or T2DM, they appear very valuable for studying the impact of deficient insulin signaling and/or hyperglycemia on learning and memory.

3.4 Metabolic syndrome/ diabetes in aging rats and genetic models of obesity

When fed *ad libitum*, Sprague-Dawley (SD) rats develop obesity, insulin resistance and dyslipidemia by 12 months of age (Barzilai and Rossetti, 1996; Narimiya et al., 1984; Reaven et al., 1983). In F344 rats, a well characterized model of aging, the effects are less consistent; insulin resistance with aging has been reported (Bracho-Romero and Reaven, 1977; Catalano et al., 2005; Park et al., 2006) but may be more moderate than in SD rats (Barzilai and Rossetti, 1995; Levin et al., 1983). Glucose tolerance tests show that peak plasma glucose levels are higher in aging F344s on a regular *ad libitum* diet, but steady state glucose levels appear unchanged (Kalant et al., 1988). Furthermore, advanced glycation end products, evidence of glucose-modified proteins, are elevated in aged F344s (Li et al., 1996). Typically, diets containing higher amounts of fat (e.g., the Western diet) tend to increase signs of metabolic syndrome in various strains (Barnard et al., 1998; Haseman et al., 2003; Keenan et al., 2005). Surprisingly, however, our recent study found that aging F344s fed a high fat diet did not develop a full metabolic syndrome or clear signs of diabetes (Pancani et al., 2013). Together, these studies suggest that some but not necessarily all components of metabolic syndrome/ diabetes develop in aging rats, indicating that rodents may be useful models for investigating how aging and the metabolic syndrome interact to affect cognition.

A number of studies have attempted to examine these mechanisms in animal models of obesity. In genetic models lacking the adipose-derived satiety hormone, leptin, a loss of function of the leptin pathway leads to hyperphagia and obesity (e.g., *Lep^{ob}*, *Lep^{db}*, *Tub^{tub}*

mice; Zucker fatty (*fa/fa*), Goto-Kakizaki, and Agouti rats). Among these obesity models, the *fa/fa* rat and the *db/db* mouse show decreased learning by 7 weeks of age on the MWM and a decrease in hippocampal LTP (Li et al., 2002). In contrast, 5–8 weeks of confirmed hyperinsulinemia and hyperglycemia did not alter spatial memory and/or LTP in Zucker diabetic fatty rats (Belanger et al., 2004). These inconsistencies might be due to several differences in the models and paradigms including age of the animal, duration of the diabetic condition, and LTP induction protocols. In addition, an important limitation of these animal models of obesity is their short lifespan and hence, it is unclear how cognition is altered with aging.

The impact of long-term high fat feeding (45% Kcal from fat) in wild-type C57Bl/6 mice has also been examined (Mielke et al., 2006). A high fat diet for 10 months significantly increased body weight, impaired glucoregulation, and altered insulin signaling in the hippocampus, but did not affect water maze learning or LTP induction. While the behavioral and electrophysiological consequences of obesity on hippocampal function in some cases appear mild or even minimal in younger animals, the question remains: would cognitive function and hippocampal physiology be impaired to a greater extent if the obesity and metabolic dysregulation were induced in aged animals?

4.0 Brain Ca^{2+} Regulation

4.1 Calcium-related biomarkers of brain aging

If insulin and other diabetes/metabolic syndrome factors do modulate brain aging/AD, then one strong candidate target through which these factors may act is brain Ca^{2+} signaling. Ca^{2+} dysregulation appears to be an important pathogenic mechanism of unhealthy brain aging and AD. Animal models and human studies have revealed brain neuronal Ca^{2+} dyshomeostasis in models of both aging and AD (for recent reviews see Bruno et al., 2012; Disterhoft and Oh, 2007; Murchison et al., 2009; Thibault et al., 2007; Toescu and Verkhratsky, 2007), findings that have led to several versions of a “ Ca^{2+} hypothesis of brain aging and dementia” (Gibson et al., 1986; Khachaturian, 1984; Landfield, 1983; Landfield and Pitler, 1984; Michaelis et al., 1984). Proposed initially in the early-mid 80’s, this view has since garnered substantial support. In particular, electrophysiological studies of hippocampal neurons have shown a consistent pattern of elevated Ca^{2+} influx and transients (Disterhoft et al., 1993; Kelly et al., 2006; Landfield, 1987; Thibault and Landfield, 1996; Thibault et al., 1998). The general hypothesis states that increased Ca^{2+} transients and Ca^{2+} -dependent processes during aging distort Ca^{2+} signaling and synaptic plasticity, leading to impaired neuronal communication, and finally to impaired cognition, memory formation and neurodegenerative changes. One of the most consistently observed Ca^{2+} and aging-dependent electrophysiological biomarkers is an aging-related increase in the amplitude and duration of the slow Ca^{2+} -dependent slow afterhyperpolarization (sAHP) (Kerr et al., 1989; Landfield and Pitler, 1984). The sAHP is triggered following a burst of action potentials and is mediated by hyperpolarizing currents via small conductance K^{+} channels activated by the Ca^{2+} influx accompanying the burst (Stocker, 2004). The age-related increase in hyperpolarization is associated with reduced neuronal excitability. The increased AHP also correlates with cognitive decline (Disterhoft et al., 1996; Tombaugh et al., 2005). Conversely, reductions in the AHP are associated with facilitation of learning and memory (Disterhoft and Oh, 2007). Increased activity of the L-type voltage-gated Ca^{2+} channel (L-VGCC) is another biomarker of hippocampal aging. With aging, Ca^{2+} influx via L-VGCCs increases significantly in aged compared to young-adult neurons, contributes to the larger AHP and is associated with cognitive impairment (Thibault and Landfield, 1996). Furthermore, we have shown that the increase in Ca^{2+} influx via L-VGCCs elevates intracellular Ca^{2+} levels, reduces synaptic plasticity (Thibault et al., 2001) and decreases spike throughput (Gant and Thibault, 2008). Recent experiments suggest that Ca^{2+}

dysregulation through increased L-VGCCs is also present in the retina of aged animals (Bissig et al., 2013).

In addition, it has recently become clear that intracellular Ca^{2+} release from activation of ryanodine receptors (RyR) on the endoplasmic reticulum is also increased in hippocampal neurons of aged rats and may act in series with L-VGCCs to amplify cytoplasmic $[\text{Ca}^{2+}]_i$ and Ca^{2+} -dependent processes in brain neurons during synaptic stimulation (Gant et al., 2011; Gant et al., 2006). Further, the increased RyR release may impair LTP (Kumar and Foster, 2005). Thus, these augmented components of Ca^{2+} signaling appear to play a major role in the declines in hippocampal synaptic plasticity, neuronal excitability and cognitive function seen during aging.

4.2. Diabetes/metabolic syndrome and altered brain calcium (Ca^{2+}) homeostasis

A number of studies suggest that Ca^{2+} regulation in the brain could be an important target of metabolic syndrome/diabetes. In an extensive series of studies, Gispen, Biessels and colleagues used STZ-treated rat models to reveal that deficient insulin signaling was associated with impaired MWM performance and weaker Ca^{2+} -dependent LTP in hippocampus (Biessels et al., 1996; Biessels et al., 1998; Kamal et al., 2003; Kamal et al., 2000). This group also was the first to note that alterations in Ca^{2+} regulation might mediate the deleterious effects of diabetes on hippocampal function and behavior (Biessels and Gispen, 1996; Biessels et al., 2002b; Gispen and Biessels, 2000). Furthermore, Verkhratsky and colleagues found that resting Ca^{2+} and mitochondrial Ca^{2+} load are increased in dorsal root ganglion neurons of hyperglycemic STZ-treated rats (Huang et al., 2002; Huang et al., 2005). Broader Ca^{2+} action potentials, larger Ca^{2+} -dependent sAHPs and perturbations in intracellular Ca^{2+} release also are observed in hippocampal slices obtained from STZ-treated diabetic animals (Huang et al., 2002; Kamal et al., 2003; Kruglikov et al., 2004). A study examining STZ-induced Ca^{2+} dysregulation specifically in the context of aging showed that chronic hyperglycemia accelerated the effect of aging in the MWM (Kamal et al., 2000). Thus, multiple studies of Ca^{2+} -dependent electrophysiological indices and learning suggest a strong link between brain Ca^{2+} dysregulation and diabetes. Nevertheless, with a few exceptions (e.g., Kamal et al., 2000), there is a paucity of studies regarding interactions of diabetes and Ca^{2+} regulation specifically in the aging brain. Consequently, it is not fully clear whether Ca^{2+} -dependent aging biomarkers are widely induced/accelerated by deficient insulin signaling or whether, conversely, such brain aging markers can be countered or prevented by insulin treatment (Chapman et al., 2012) or insulin-sensitizing agents.

5.0. Can enhanced insulin signaling counteract aging-related hippocampal Ca^{2+} dyshomeostasis?

As reviewed above, there is extensive evidence indicating that insulin resistance in metabolic syndrome, T2DM and STZ-mediated depletion of insulin are associated with cognitive decline and/or risk for AD. Each of these disorders can be viewed as a condition reflecting deficient insulin signaling, an alteration also associated with brain Ca^{2+} dysregulation. On the other hand, increased insulin efficacy is associated with improved brain function. To elucidate mechanisms of these insulin effects, we have been assessing a version of the hypothesis (Biessels et al., 2002b) that diabetes targets hippocampal Ca^{2+} -dependent processes that are dysregulated with aging. This hypothesis makes several predictions, including the following: Insulin or insulin-sensitizing agents 1) should target components of Ca^{2+} signaling that are altered in aging; and 2) should counteract the effects seen with aging.

In testing these predictions, we have carried out a series of studies to determine if insulin-sensitizers (i.e., TZDs) directly reduce calcium levels in brain cells. Our results show that in cultured hippocampal neurons, Ca^{2+} levels attained during short-term exposure to the glutamate receptor agonist NMDA can be attenuated by pretreatment with the TZD pioglitazone (Fig. 1). Electrophysiological analyses revealed that 24 h pioglitazone was also able to reduce Ca^{2+} current flux through the NMDA receptor (Fig. 2). The TZD rosiglitazone, while unable to alter NMDA-mediated calcium levels or currents, was able to reduce influx through voltage-gated calcium channels (Pancani et al., 2009). These results indicate TZDs can modulate Ca^{2+} -dependent pathways in the brain, particularly those calcium sources known to be increased with age (Danysz and Parsons, 2003; Thibault and Landfield, 1996). Using similar culture conditions, we also tested the possibility that the TZD pioglitazone could modulate glucose utilization in neurons and astrocytes. After first confirming that potassium-mediated increases in calcium levels could acutely and rapidly increase glucose utilization in neurons, we showed that pioglitazone reduced glucose utilization in neurons but increased it in astrocytes (Pancani et al., 2011). These results are consistent with a recent study of pioglitazone effects in the brain showing that pioglitazone could reduce glucose utilization *in vivo* (Galea et al., 2006).

In other studies of TZDs, we found that the AHP was reduced in aged animals treated chronically with pioglitazone (Fig. 3 - (Blalock et al., 2010)) and that pioglitazone improved LTP maintenance in the 3xTg animal model of Alzheimer's disease (Fig. 4 - (Searcy et al., 2012)). Recently we also found that in the hippocampus, the Ca^{2+} -dependent AHP is reduced by insulin (Pancani et al., 2013). Further, a long-term high fat diet reduced the AHP's sensitivity to insulin in aging F344 rats, (Fig. 5), suggesting that the insulin receptor in brain may be a target of dyslipidemia. Conversely, caloric restriction, which enhances insulin signaling, has been shown to improve Ca^{2+} dysregulation in CA1 pyramidal neurons from aged F344 rats (Hemond and Jaffe, 2005). Together, these results are consistent with the predictions highlighted above that insulin or insulin-sensitizing agents can target components of Ca^{2+} signaling that are altered in aging.

6.0. Conclusions

The increasing evidence summarized in this review linking cognitive impairment to altered insulin signaling in human conditions such as metabolic syndrome, obesity and T2DM and in animal models, makes clear that it is imperative that we identify the mechanisms underlying this association. There is a current epidemic of these metabolic conditions, which are largely diseases of aging, with over 63% of new diabetes cases occurring between the ages of 40–64 (US CDC; WHO) (Wild et al., 2004). Considering the large increase in the fractional aging population already being projected, it is apparent that this epidemic substantially increases the likelihood that society is facing a potential tidal wave of AD patients.

A common feature of these disorders and models is deficient insulin signaling, either because of insulin resistance in metabolic syndrome or insulin depletion in diabetes. Further, manipulating insulin signaling in humans and animals directly impacts cognitive functioning. Therefore, one approach to identifying underlying mechanisms is analyzing the effects of insulin and insulin-modifying agents on neural tissues, which is being done by several groups. In particular, some studies have focused on the interplay of diabetes and Ca^{2+} dysregulation, or diabetes and aging, but very few have assessed these factors together. We are pursuing a strategy of testing whether enhanced insulin signaling can counteract the effects of aging on hippocampal Ca^{2+} regulation. To date, results are consistent with this possibility and therefore, suggest that the strategy may prove fruitful and yield novel therapeutic approaches for counteracting unhealthy brain aging and risk of AD.

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References

- Agrawal R, Tyagi E, Shukla R, Nath C. Insulin receptor signaling in rat hippocampus: a study in STZ (ICV) induced memory deficit model. *Eur Neuropsychopharmacol.* 2011; 21:261–273. [PubMed: 21195590]
- Austad SN. Aging and caloric restriction: human effects and mode of action. *Neurobiol Aging.* 1995; 16:851–852. discussion 855–856. [PubMed: 8532122]
- Awad N, Gagnon M, Messier C. The relationship between impaired glucose tolerance, type 2 diabetes, and cognitive function. *J Clin Exp Neuropsychol.* 2004; 26:1044–1080. [PubMed: 15590460]
- Axen KV, Dikeakos A, Sclafani A. High dietary fat promotes syndrome X in nonobese rats. *J Nutr.* 2003; 133:2244–2249. [PubMed: 12840187]
- Baranowska B, Bik W, Baranowska Bik A, Wolinska Witort E, Szybinska A, Martynska L, Chmielowska M. Neuroendocrine control of metabolic homeostasis in polish centenarians. *J Physiol Pharmacol.* 2006; 57(Suppl 6):55–61. [PubMed: 17228087]
- Barbieri M, Rizzo MR, Manzella D, Paolisso G. Age related insulin resistance: is it an obligatory finding? The lesson from healthy centenarians. *Diabetes Metab Res Rev.* 2001; 17:19–26. [PubMed: 11241888]
- Barnard RJ, Roberts CK, Varon SM, Berger JJ. Diet induced insulin resistance precedes other aspects of the metabolic syndrome. *J Appl Physiol.* 1998; 84:1311–1315. [PubMed: 9516198]
- Barzilai N, Rossetti L. Relationship between changes in body composition and insulin responsiveness in models of the aging rat. *Am J Physiol.* 1995; 269:E591–597. [PubMed: 7573438]
- Barzilai N, Rossetti L. Age related changes in body composition are associated with hepatic insulin resistance in conscious rats. *Am J Physiol.* 1996; 270:E930–936. [PubMed: 8764175]
- Baura GD, Foster DM, Kaiyala K, Porte D Jr, Kahn SE, Schwartz MW. Insulin transport from plasma into the central nervous system is inhibited by dexamethasone in dogs. *Diabetes.* 1996; 45:86–90. [PubMed: 8522065]
- Baydas G, Nedzvetskii VS, Nerush PA, Kirichenko SV, Yoldas T. Altered expression of NCAM in hippocampus and cortex may underlie memory and learning deficits in rats with streptozotocin induced diabetes mellitus. *Life sciences.* 2003; 73:1907–1916. [PubMed: 12899916]
- Belanger A, Lavoie N, Trudeau F, Massicotte G, Gagnon S. Preserved LTP and water maze learning in hyperglycaemic hyperinsulinemic ZDF rats. *Physiol Behav.* 2004; 83:483–494. [PubMed: 15581671]
- Benedict C, Hallschmid M, Schmitz K, Schultes B, Ratter F, Fehm HL, Born J, Kern W. Intranasal insulin improves memory in humans: superiority of insulin aspart. *Neuropsychopharmacology.* 2007; 32:239–243. [PubMed: 16936707]
- Biessels G, Gispen WH. The calcium hypothesis of brain aging and neurodegenerative disorders: significance in diabetic neuropathy. *Life Sci.* 1996; 59:379–387. [PubMed: 8761325]
- Biessels GJ, Deary IJ, Ryan CM. Cognition and diabetes: a lifespan perspective. *Lancet Neurol.* 2008; 7:184–190. [PubMed: 18207116]
- Biessels GJ, Kamal A, Ramakers GM, Urban IJ, Spruijt BM, Erkelens DW, Gispen WH. Place learning and hippocampal synaptic plasticity in streptozotocin induced diabetic rats. *Diabetes.* 1996; 45:1259–1266. [PubMed: 8772732]
- Biessels GJ, Kamal A, Urban IJ, Spruijt BM, Erkelens DW, Gispen WH. Water maze learning and hippocampal synaptic plasticity in streptozotocin diabetic rats: effects of insulin treatment. *Brain Res.* 1998; 800:125–135. [PubMed: 9685609]
- Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol.* 2006; 5:64–74. [PubMed: 16361024]
- Biessels GJ, ter Laak MP, Hamers FP, Gispen WH. Neuronal Ca²⁺ dysregulation in diabetes mellitus. *European journal of pharmacology.* 2002a; 447:201–209. [PubMed: 12151012]

- Biessels GJ, van der Heide LP, Kamal A, Bleys RL, Gispen WH. Ageing and diabetes: implications for brain function. *Eur J Pharmacol.* 2002b; 441:1–14. [PubMed: 12007915]
- Bissig D, Goebel D, Berkowitz BA. Diminished vision in healthy aging is associated with increased retinal L type voltage gated calcium channel ion influx. *PLoS ONE.* 2013; 8:e56340. [PubMed: 23457553]
- Bizon JL, LaSarge CL, Montgomery KS, McDermott AN, Setlow B, Griffith WH. Spatial reference and working memory across the lifespan of male Fischer 344 rats. *Neurobiology of aging.* 2009; 30:646–655. [PubMed: 17889407]
- Blalock EM, Phelps JT, Pancani T, Searcy JL, Anderson KL, Gant JC, Popovic J, Avdiushko MG, Cohen DA, Chen KC, Porter NM, Thibault O. Effects of long term pioglitazone treatment on peripheral and central markers of aging. *PLoS ONE.* 2010; 5:e10405. [PubMed: 20454453]
- Bracho Romero E, Reaven GM. Effect of age and weight on plasma glucose and insulin responses in the rat. *J Am Geriatr Soc.* 1977; 25:299–302. [PubMed: 864176]
- Brinton RD. Estrogen regulation of glucose metabolism and mitochondrial function: therapeutic implications for prevention of Alzheimer's disease. *Adv Drug Deliv Rev.* 2008; 60:1504–1511. [PubMed: 18647624]
- Bruno AM, Huang JY, Bennett DA, Marr RA, Hastings ML, Stutzmann GE. Altered ryanodine receptor expression in mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging.* 2012; 33:1001, e1001–1006. [PubMed: 21531043]
- Burns JM, Honea RA, Vidoni ED, Hutfles LJ, Brooks WM, Swerdlow RH. Insulin is differentially related to cognitive decline and atrophy in Alzheimer's disease and aging. *Biochim Biophys Acta.* 2012; 1822:333–339. [PubMed: 21745566]
- Catalano KJ, Bergman RN, Ader M. Increased susceptibility to insulin resistance associated with abdominal obesity in aging rats. *Obes Res.* 2005; 13:11–20. [PubMed: 15761159]
- Chapman CD, Frey WH 2nd, Craft S, Danielyan L, Hallschmid M, Schioth HB, Benedict C. Intranasal Treatment of Central Nervous System Dysfunction in Humans. *Pharm Res.* 2012
- Cholerton B, Baker LD, Craft S. Insulin resistance and pathological brain ageing. *Diabet Med.* 2011; 28:1463–1475. [PubMed: 21974744]
- Cole GM, Frautschy SA. The role of insulin and neurotrophic factor signaling in brain aging and Alzheimer's Disease. *Exp Gerontol.* 2007; 42:10–21. [PubMed: 17049785]
- Craft S. Insulin resistance syndrome and Alzheimer's disease: age and obesity related effects on memory, amyloid, and inflammation. *Neurobiol Aging.* 2005; 26(Suppl 1):65–69. [PubMed: 16266773]
- Craft S. Insulin resistance syndrome and Alzheimer disease: pathophysiologic mechanisms and therapeutic implications. *Alzheimer disease and associated disorders.* 2006; 20:298–301. [PubMed: 17132977]
- Craft S. Insulin resistance and Alzheimer's disease pathogenesis: potential mechanisms and implications for treatment. *Current Alzheimer research.* 2007; 4:147–152. [PubMed: 17430239]
- Craft S, Cholerton B, Baker LD. Insulin and Alzheimer's Disease: Untangling the Web. *J Alzheimers Dis.* 2012
- Craft S, Peskind E, Schwartz MW, Schellenberg GD, Raskind M, Porte D Jr. Cerebrospinal fluid and plasma insulin levels in Alzheimer's disease: relationship to severity of dementia and apolipoprotein E genotype. *Neurology.* 1998; 50:164–168. [PubMed: 9443474]
- Craft S, Watson GS. Insulin and neurodegenerative disease: shared and specific mechanisms. *Lancet Neurol.* 2004; 3:169–178. [PubMed: 14980532]
- Curtis R, Geesaman BJ, DiStefano PS. Ageing and metabolism: drug discovery opportunities. *Nat Rev Drug Discov.* 2005; 4:569–580. [PubMed: 15976816]
- Danysz W, Parsons CG. The NMDA receptor antagonist memantine as a symptomatological and neuroprotective treatment for Alzheimer's disease: preclinical evidence. *Int J Geriatr Psychiatry.* 2003; 18:S23–32. [PubMed: 12973747]
- de la Monte SM. Brain insulin resistance and deficiency as therapeutic targets in Alzheimer's disease. *Curr Alzheimer Res.* 2012; 9:35–66. [PubMed: 22329651]

- de la Monte SM, Tong M, Lester Coll N, Plater M Jr, Wands JR. Therapeutic rescue of neurodegeneration in experimental type 3 diabetes: Relevance to Alzheimer's disease. *J Alzheimers Dis.* 2006; 10:89–109. [PubMed: 16988486]
- de Leon MJ, Mosconi L, Blennow K, DeSanti S, Zinkowski R, Mehta PD, Pratico D, Tsui W, Saint Louis LA, Sobanska L, Brys M, Li Y, Rich K, Rinne J, Rusinek H. Imaging and CSF studies in the preclinical diagnosis of Alzheimer's disease. *Ann N Y Acad Sci.* 2007; 1097:114–145. [PubMed: 17413016]
- Disterhoft JF, Moyer JR Jr, Thompson LT, Kowalska M. Functional aspects of calcium channel modulation. *Clin Neuropharmacol.* 1993; 16:S12–24. [PubMed: 8390916]
- Disterhoft JF, Oh MM. Alterations in intrinsic neuronal excitability during normal aging. *Aging Cell.* 2007; 6:327–336. [PubMed: 17517042]
- Disterhoft JF, Thompson LT, Moyer JR Jr, Mogul DJ. Calcium dependent afterhyperpolarization and learning in young and aging hippocampus. *Life Sci.* 1996; 59:413–420. [PubMed: 8761329]
- Dou JT, Chen M, Dufour F, Alkon DL, Zhao WQ. Insulin receptor signaling in long term memory consolidation following spatial learning. *Learning & memory (Cold Spring Harbor, NY).* 2005; 12:646–655.
- Dresner A, Laurent D, Marcucci M, Griffin ME, Dufour S, Cline GW, Slezak LA, Andersen DK, Hundal RS, Rothman DL, Petersen KF, Shulman GI. Effects of free fatty acids on glucose transport and IRS 1 associated phosphatidylinositol 3 kinase activity. *J Clin Invest.* 1999; 103:253–259. [PubMed: 9916137]
- Duelli R, Maurer MH, Staudt R, Heiland S, Duembgen L, Kuschinsky W. Increased cerebral glucose utilization and decreased glucose transporter Glut1 during chronic hyperglycemia in rat brain. *Brain Res.* 2000; 858:338–347. [PubMed: 10708685]
- Duelli R, Schrock H, Kuschinsky W, Hoyer S. Intracerebroventricular injection of streptozotocin induces discrete local changes in cerebral glucose utilization in rats. *Int J Dev Neurosci.* 1994; 12:737–743. [PubMed: 7747600]
- Eberling JL, Nordahl TE, Kusubov N, Reed BR, Budinger TF, Jagust WJ. Reduced temporal lobe glucose metabolism in aging. *J Neuroimaging.* 1995; 5:178–182. [PubMed: 7626826]
- Facchini FS, Hua N, Abbasi F, Reaven GM. Insulin resistance as a predictor of age related diseases. *J Clin Endocrinol Metab.* 2001; 86:3574–3578. [PubMed: 11502781]
- Fishel MA, Watson GS, Montine TJ, Wang Q, Green PS, Kulstad JJ, Cook DG, Peskind ER, Baker LD, Goldgaber D, Nie W, Asthana S, Plymate SR, Schwartz MW, Craft S. Hyperinsulinemia provokes synchronous increases in central inflammation and beta amyloid in normal adults. *Archives of neurology.* 2005; 62:1539–1544. [PubMed: 16216936]
- Folli F, Ghidella S, Bonfanti L, Kahn CR, Merighi A. The early intracellular signaling pathway for the insulin/insulin like growth factor receptor family in the mammalian central nervous system. *Mol Neurobiol.* 1996; 13:155–183. [PubMed: 8938649]
- Furuhashi M, Tuncman G, Gorgun CZ, Makowski L, Atsumi G, Vaillancourt E, Kono K, Babaev VR, Fazio S, Linton MF, Sulsky R, Robl JA, Parker RA, Hotamisligil GS. Treatment of diabetes and atherosclerosis by inhibiting fatty acid binding protein aP2. *Nature.* 2007; 447:959–965. [PubMed: 17554340]
- Gabriely I, Ma XH, Yang XM, Atzmon G, Rajala MW, Berg AH, Scherer P, Rossetti L, Barzilai N. Removal of visceral fat prevents insulin resistance and glucose intolerance of aging: an adipokine mediated process? *Diabetes.* 2002; 51:2951–2958. [PubMed: 12351432]
- Galea E, Feinstein DL, Lacombe P. Pioglitazone does not increase cerebral glucose utilisation in a murine model of Alzheimer's disease and decreases it in wild type mice. *Diabetologia.* 2006; 49:2153–2161. [PubMed: 16830140]
- Gant JC, Chen KC, Norris CM, Kadish I, Thibault O, Blalock EM, Porter NM, Landfield PW. Disrupting function of FK506 binding protein 1b/12.6 induces the Ca(2)+ dysregulation aging phenotype in hippocampal neurons. *J Neurosci.* 2011; 31:1693–1703. [PubMed: 21289178]
- Gant JC, Sama MM, Landfield PW, Thibault O. Early and simultaneous emergence of multiple hippocampal biomarkers of aging is mediated by Ca2+ induced Ca2+ release. *J Neurosci.* 2006; 26:3482–3490. [PubMed: 16571755]

- Gant JC, Thibault O. Action potential throughput in aged rat hippocampal neurons: Regulation by selective forms of hyperpolarization. *Neurobiol Aging*. 2008
- Gardoni F, Kamal A, Bellone C, Biessels GJ, Ramakers GM, Cattabeni F, Gispen WH, Di Luca M. Effects of streptozotocin diabetes on the hippocampal NMDA receptor complex in rats. *J Neurochem*. 2002; 80:438–447. [PubMed: 11908465]
- Gasparini L, Netzer WJ, Greengard P, Xu H. Does insulin dysfunction play a role in Alzheimer's disease? *Trends Pharmacol Sci*. 2002; 23:288–293. [PubMed: 12084635]
- Gemma C, Stellwagen H, Fister M, Coultrap SJ, Mesches MH, Browning MD, Bickford PC. Rosiglitazone improves contextual fear conditioning in aged rats. *Neuroreport*. 2004; 15:2255–2259. [PubMed: 15371745]
- Gibson G, Perrino P, Dienel GA. In vivo brain calcium homeostasis during aging. *Mech Ageing Dev*. 1986; 37:1–12. [PubMed: 3821184]
- Gispen WH, Biessels GJ. Cognition and synaptic plasticity in diabetes mellitus. *Trends Neurosci*. 2000; 23:542–549. [PubMed: 11074263]
- Griffin ME, Marcucci MJ, Cline GW, Bell K, Barucci N, Lee D, Goodyear LJ, Kraegen EW, White MF, Shulman GI. Free fatty acid induced insulin resistance is associated with activation of protein kinase C θ and alterations in the insulin signaling cascade. *Diabetes*. 1999; 48:1270–1274. [PubMed: 10342815]
- Grunblatt E, Salkovic Petrisic M, Osmanovic J, Riederer P, Hoyer S. Brain insulin system dysfunction in streptozotocin intracerebroventricularly treated rats generates hyperphosphorylated tau protein. *J Neurochem*. 2007; 101:757–770. [PubMed: 17448147]
- Gustafson D. Adiposity indices and dementia. *Lancet neurology*. 2006; 5:713–720. [PubMed: 16857578]
- Haseman JK, Ney E, Nyska A, Rao GN. Effect of diet and animal care/housing protocols on body weight, survival, tumor incidences, and nephropathy severity of F344 rats in chronic studies. *Toxicol Pathol*. 2003; 31:674–681. [PubMed: 14585736]
- Hemond P, Jaffe DB. Caloric restriction prevents aging associated changes in spike mediated Ca^{2+} accumulation and the slow afterhyperpolarization in hippocampal CA1 pyramidal neurons. *Neuroscience*. 2005; 135:413–420. [PubMed: 16112472]
- Huang TJ, Sayers NM, Fernyhough P, Verkhatsky A. Diabetes induced alterations in calcium homeostasis in sensory neurones of streptozotocin diabetic rats are restricted to lumbar ganglia and are prevented by neurotrophin 3. *Diabetologia*. 2002; 45:560–570. [PubMed: 12032634]
- Huang TJ, Sayers NM, Verkhatsky A, Fernyhough P. Neurotrophin 3 prevents mitochondrial dysfunction in sensory neurons of streptozotocin diabetic rats. *Exp Neurol*. 2005; 194:279–283. [PubMed: 15899264]
- Ingram DK, Anson RM, de Cabo R, Mamczarz J, Zhu M, Mattison J, Lane MA, Roth GS. Development of calorie restriction mimetics as a longevity strategy. *Ann N Y Acad Sci*. 2004; 1019:412–423. [PubMed: 15247056]
- Issa AM, Rowe W, Gauthier S, Meaney MJ. Hypothalamic pituitary adrenal activity in aged, cognitively impaired and cognitively unimpaired rats. *J Neurosci*. 1990; 10:3247–3254. [PubMed: 2170594]
- Itani SI, Ruderman NB, Schmieder F, Boden G. Lipid induced insulin resistance in human muscle is associated with changes in diacylglycerol, protein kinase C, and IkappaB α . *Diabetes*. 2002; 51:2005–2011. [PubMed: 12086926]
- Janson J, Laedtke T, Parisi JE, O'Brien P, Petersen RC, Butler PC. Increased risk of type 2 diabetes in Alzheimer disease. *Diabetes*. 2004; 53:474–481. [PubMed: 14747300]
- Jin Z, Jin Y, Kumar Mendu S, Degerman E, Groop L, Birnir B. Insulin reduces neuronal excitability by turning on GABA(A) channels that generate tonic current. *PLoS ONE*. 2011; 6:e16188. [PubMed: 21264261]
- Kalant N, Stewart J, Kaplan R. Effect of diet restriction on glucose metabolism and insulin responsiveness in aging rats. *Mech Ageing Dev*. 1988; 46:89–104. [PubMed: 3067001]
- Kamal A, Artola A, Biessels GJ, Gispen WH, Ramakers GM. Increased spike broadening and slow afterhyperpolarization in CA1 pyramidal cells of streptozotocin induced diabetic rats. *Neuroscience*. 2003; 118:577–583. [PubMed: 12699792]

- Kamal A, Biessels GJ, Duis SE, Gispen WH. Learning and hippocampal synaptic plasticity in streptozotocin diabetic rats: interaction of diabetes and ageing. *Diabetologia*. 2000; 43:500–506. [PubMed: 10819245]
- Kamal A, Ramakers GM, Gispen WH, Biessels GJ. Effect of chronic intracerebroventricular insulin administration in rats on the peripheral glucose metabolism and synaptic plasticity of CA1 hippocampal neurons. *Brain Res*. 2012; 1435:99–104. [PubMed: 22206925]
- Keenan KP, Hoe CM, Mixson L, McCoy CL, Coleman JB, Mattson BA, Ballam GA, Gumprecht LA, Soper KA. Diabetes: a polygenic model of dietary induced obesity from ad libitum overfeeding of Sprague Dawley rats and its modulation by moderate and marked dietary restriction. *Toxicol Pathol*. 2005; 33:650–674. [PubMed: 16207639]
- Keenan KP, Soper KA, Hertzog PR, Gumprecht LA, Smith PF, Mattson BA, Ballam GC, Clark RL. Diet, overfeeding, and moderate dietary restriction in control Sprague Dawley rats: II. Effects on age related proliferative and degenerative lesions. *Toxicol Pathol*. 1995; 23:287–302. [PubMed: 7659953]
- Kelly KM, Nadon NL, Morrison JH, Thibault O, Barnes CA, Blalock EM. The neurobiology of aging. *Epilepsy Res*. 2006; 68(Suppl 1):S5–20. [PubMed: 16386406]
- Kerr DS, Campbell LW, Hao SY, Landfield PW. Corticosteroid modulation of hippocampal potentials: increased effect with aging. *Science*. 1989; 245:1505–1509. [PubMed: 2781293]
- Khachaturian, ZS. Towards theories of brain aging. In: Kay, DS.; Burrows, GW., editors. *Handbook of Studies on Psychiatry and Old Age*. Elsevier; Amsterdam: 1984. p. 7-30.
- Kim JK, Fillmore JJ, Chen Y, Yu C, Moore IK, Pypaert M, Lutz EP, Kako Y, Velez Carrasco W, Goldberg IJ, Breslow JL, Shulman GI. Tissue specific overexpression of lipoprotein lipase causes tissue specific insulin resistance. *Proc Natl Acad Sci U S A*. 2001; 98:7522–7527. [PubMed: 11390966]
- Klein S. Is visceral fat responsible for the metabolic abnormalities associated with obesity?: implications of omentectomy. *Diabetes Care*. 2010; 33:1693–1694. [PubMed: 20587732]
- Korol DL, Gold PE. Glucose, memory, and aging. *Am J Clin Nutr*. 1998; 67:764S, 771S. [PubMed: 9537626]
- Kruglikov I, Gryshchenko O, Shutov L, Kostyuk E, Kostyuk P, Voitenko N. Diabetes induced abnormalities in ER calcium mobilization in primary and secondary nociceptive neurons. *Pflugers Arch*. 2004; 448:395–401. [PubMed: 15048576]
- Kulstad, J.; Green, PS.; Cook, DG.; Watson, GS.; Reger, M.; Cholerton, B.; Baker, LD.; Plymate, SR.; Asthana, S.; Fishel, M.; Kahn, SE.; Craft, S. Effects of Rosiglitazone treatment on serum Amyloid Beta 1-40 and 1-42 in patients with early Alzheimer's disease. *Neurobiology of Aging; 9th International Conference on Alzheimer's Disease and Related Disorders*; 2004. p. 354Abstract p3-012
- Kulstad JJ, Green PS, Cook DG, Watson GS, Reger MA, Baker LD, Plymate SR, Asthana S, Rhoads K, Mehta PD, Craft S. Differential modulation of plasma beta amyloid by insulin in patients with Alzheimer disease. *Neurology*. 2006; 66:1506–1510. [PubMed: 16717209]
- Kumar A, Foster TC. Intracellular calcium stores contribute to increased susceptibility to LTD induction during aging. *Brain Res*. 2005; 1031:125–128. [PubMed: 15621020]
- Landfield, PW. Mechanisms of altered neural function during aging. In: Gispen, WH.; Traber, J., editors. *Aging of the brain; Proceedings of the first international Tropon symposium on brain aging, held in Cologne, Federal Republic of Germany*; Amsterdam: Elsevier Science Publishers; 1983. p. 51-71.
- Landfield PW. 'Increased calcium current' hypothesis of brain aging. *Neurobiol Aging*. 1987; 8:346–347. [PubMed: 3627350]
- Landfield PW, Baskin RK, Pitler TA. Brain aging correlates: retardation by hormonal pharmacological treatments. *Science (New York, NY)*. 1981; 214:581–584.
- Landfield PW, Blalock EM, Chen KC, Porter NM. A new glucocorticoid hypothesis of brain aging: implications for Alzheimer's disease. *Current Alzheimer research*. 2007; 4:205–212. [PubMed: 17430248]
- Landfield PW, Pitler TA. Prolonged Ca²⁺ dependent afterhyperpolarizations in hippocampal neurons of aged rats. *Science*. 1984; 226:1089–1092. [PubMed: 6494926]

- Lannert H, Hoyer S. Intracerebroventricular administration of streptozotocin causes long term diminutions in learning and memory abilities and in cerebral energy metabolism in adult rats. *Behav Neurosci*. 1998; 112:1199–1208. [PubMed: 9829797]
- Lester Coll N, Rivera EJ, Soscia SJ, Doiron K, Wands JR, de la Monte SM. Intracerebral streptozotocin model of type 3 diabetes: relevance to sporadic Alzheimer's disease. *J Alzheimers Dis*. 2006; 9:13–33. [PubMed: 16627931]
- Levin BE, Triscari J, Sullivan AC. Relationship between sympathetic activity and diet induced obesity in two rat strains. *Am J Physiol*. 1983; 245:R364–371. [PubMed: 6614206]
- Li H, Wei Q. Conformation changes in brain calcineurin in diabetic rats with or without treatment with vanadyl sulfate. *IUBMB Life*. 2001; 51:373–376. [PubMed: 11758805]
- Li XL, Aou S, Oomura Y, Hori N, Fukunaga K, Hori T. Impairment of long term potentiation and spatial memory in leptin receptor deficient rodents. *Neuroscience*. 2002; 113:607–615. [PubMed: 12150780]
- Li YM, Steffes M, Donnelly T, Liu C, Fuh H, Basgen J, Bucala R, Vlassara H. Prevention of cardiovascular and renal pathology of aging by the advanced glycation inhibitor aminoguanidine. *Proc Natl Acad Sci U S A*. 1996; 93:3902–3907. [PubMed: 8632987]
- Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. *Diabetologia*. 2011; 54:2506–2514. [PubMed: 21656330]
- Luchsinger JA, Small S, Biessels GJ. Should we target insulin resistance to prevent dementia due to Alzheimer disease? *Arch Neurol*. 2011; 68:17–18. [PubMed: 21220672]
- Lupien SJ, de Leon M, de Santi S, Convit A, Tarshish C, Nair NP, Thakur M, McEwen BS, Hauger RL, Meaney MJ. Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nature neuroscience*. 1998; 1:69–73.
- Magarinos AM, McEwen BS. Experimental diabetes in rats causes hippocampal dendritic and synaptic reorganization and increased glucocorticoid reactivity to stress. *Proc Natl Acad Sci U S A*. 2000; 97:11056–11061. [PubMed: 11005876]
- Martin B, Mattson MP, Maudsley S. Caloric restriction and intermittent fasting: two potential diets for successful brain aging. *Ageing Res Rev*. 2006; 5:332–353. [PubMed: 16899414]
- Mattson MP. Emerging neuroprotective strategies for Alzheimer's disease: dietary restriction, telomerase activation, and stem cell therapy. *Exp Gerontol*. 2000; 35:489–502. [PubMed: 10959037]
- McEwen BS, de Leon MJ, Lupien SJ, Meaney MJ. Corticosteroids, the Aging Brain and Cognition. *Trends in endocrinology and metabolism: TEM*. 1999; 10:92–96. [PubMed: 10322401]
- McNay EC. The impact of recurrent hypoglycemia on cognitive function in aging. *Neurobiol Aging*. 2005; 26(Suppl 1):76–79. [PubMed: 16236383]
- Messier C, Tsiakas M, Gagnon M, Desrochers A, Awad N. Effect of age and glucoregulation on cognitive performance. *Neurobiol Aging*. 2003; 24:985–1003. [PubMed: 12928059]
- Michaelis ML, Johe K, Kitos TE. Age dependent alterations in synaptic membrane systems for Ca²⁺ regulation. *Mech Ageing Dev*. 1984; 25:215–225. [PubMed: 6144821]
- Mielke JG, Nicolitch K, Avellaneda V, Earlam K, Ahuja T, Mealing G, Messier C. Longitudinal study of the effects of a high fat diet on glucose regulation, hippocampal function, and cerebral insulin sensitivity in C57BL/6 mice. *Behav Brain Res*. 2006; 175:374–382. [PubMed: 17081630]
- Mosconi L, Pupi A, De Cristofaro MT, Fayyaz M, Sorbi S, Herholz K. Functional interactions of the entorhinal cortex: an 18F FDG PET study on normal aging and Alzheimer's disease. *J Nucl Med*. 2004; 45:382–392. [PubMed: 15001677]
- Murchison D, McDermott AN, Lasarge CL, Peebles KA, Bizon JL, Griffith WH. Enhanced calcium buffering in F344 rat cholinergic basal forebrain neurons is associated with age related cognitive impairment. *J Neurophysiol*. 2009; 102:2194–2207. [PubMed: 19675291]
- Narimiya M, Azhar S, Dolkas CB, Mondon CE, Sims C, Wright DW, Reaven GM. Insulin resistance in older rats. *Am J Physiol*. 1984; 246:E397–404. [PubMed: 6426315]
- Nitsch R, Hoyer S. Local action of the diabetogenic drug, streptozotocin, on glucose and energy metabolism in rat brain cortex. *Neurosci Lett*. 1991; 128:199–202. [PubMed: 1834965]

- O'Malley D, Shanley LJ, Harvey J. Insulin inhibits rat hippocampal neurones via activation of ATP sensitive K⁺ and large conductance Ca²⁺ activated K⁺ channels. *Neuropharmacology*. 2003; 44:855–863. [PubMed: 12726817]
- Olshansky SJ, Passaro DJ, Hershow RC, Layden J, Carnes BA, Brody J, Hayflick L, Butler RN, Allison DB, Ludwig DS. A potential decline in life expectancy in the United States in the 21st century. *N Engl J Med*. 2005; 352:1138–1145. [PubMed: 15784668]
- Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: The Rotterdam Study. *Neurology*. 1999; 53:1937–1942. [PubMed: 10599761]
- Palovcik RA, Phillips MI, Kappy MS, Raizada MK. Insulin inhibits pyramidal neurons in hippocampal slices. *Brain Res*. 1984; 309:187–191. [PubMed: 6386100]
- Pancani T, Anderson KL, Brewer LD, Kadish I, Demoll C, Landfield PW, Blalock EM, Porter NM, Thibault O. Effect of high fat diet on metabolic indices, cognition, and neuronal physiology in aging F344 rats. *Neurobiol Aging*. 2013
- Pancani T, Anderson KL, Porter NM, Thibault O. Imaging of a glucose analog, calcium and NADH in neurons and astrocytes: Dynamic responses to depolarization and sensitivity to pioglitazone. *Cell Calcium*. 2011; 50:548–558. [PubMed: 21978418]
- Pancani T, Phelps JT, Searcy JL, Kilgore MW, Chen KC, Porter NM, Thibault O. Distinct modulation of voltage gated and ligand gated Ca²⁺ currents by PPAR gamma agonists in cultured hippocampal neurons. *J Neurochem*. 2009; 109:1800–1811. [PubMed: 19453298]
- Park CR, Seeley RJ, Craft S, Woods SC. Intracerebroventricular insulin enhances memory in a passive avoidance task. *Physiol Behav*. 2000; 68:509–514. [PubMed: 10713291]
- Park S, Komatsu T, Hayashi H, Yamaza H, Chiba T, Higami Y, Kuramoto K, Shimokawa I. Calorie restriction initiated at middle age improved glucose tolerance without affecting age related impairments of insulin signaling in rat skeletal muscle. *Exp Gerontol*. 2006; 41:837–845. [PubMed: 16920310]
- Pathan AR, Viswanad B, Sonkusare SK, Ramarao P. Chronic administration of pioglitazone attenuates intracerebroventricular streptozotocin induced memory impairment in rats. *Life Sci*. 2006
- Pedersen WA, McMillan PJ, Kulstad JJ, Leverenz JB, Craft S, Haynatzki GR. Rosiglitazone attenuates learning and memory deficits in Tg2576 Alzheimer mice. *Experimental neurology*. 2006; 199:265–273. [PubMed: 16515786]
- Perseghin G, Petersen K, Shulman GI. Cellular mechanism of insulin resistance: potential links with inflammation. *Int J Obes Relat Metab Disord*. 2003; 27(Suppl 3):S6–11. [PubMed: 14704736]
- Petro AE, Cotter J, Cooper DA, Peters JC, Surwit SJ, Surwit RS. Fat, carbohydrate, and calories in the development of diabetes and obesity in the C57BL/6J mouse. *Metabolism*. 2004; 53:454–457. [PubMed: 15045691]
- Pirola GG, Grillo CA, Reznikov LR, Adams S, McEwen BS, Charron MJ, Reagan LP. Corticosterone impairs insulin stimulated translocation of GLUT4 in the rat hippocampus. *Neuroendocrinology*. 2007; 85:71–80. [PubMed: 17426391]
- Plaschke K, Muller D, Hoyer S. Insulin resistant brain state (IRBS) changes membrane composition of fatty acids in temporal and entorhinal brain cortices of rats: relevance to sporadic Alzheimer's disease? *J Neural Transm*. 2010; 117:1419–1422. [PubMed: 21136123]
- Popovic M, Biessels GJ, Isaacson RL, Gispen WH. Learning and memory in streptozotocin induced diabetic rats in a novel spatial/object discrimination task. *Behavioural brain research*. 2001; 122:201–207. [PubMed: 11334650]
- Reagan LP. Glucose, stress, and hippocampal neuronal vulnerability. *Int Rev Neurobiol*. 2002; 51:289–324. [PubMed: 12420363]
- Reaven E, Wright D, Mondon CE, Solomon R, Ho H, Reaven GM. Effect of age and diet on insulin secretion and insulin action in the rat. *Diabetes*. 1983; 32:175–180. [PubMed: 6337897]
- Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes*. 1988; 37:1595–1607. [PubMed: 3056758]
- Reaven GM. The insulin resistance syndrome: definition and dietary approaches to treatment. *Annual review of nutrition*. 2005; 25:391–406.

- Reger MA, Watson GS, Green PS, Wilkinson CW, Baker LD, Cholerton B, Fishel MA, Plymate SR, Breitner JC, DeGroodt W, Mehta P, Craft S. Intranasal insulin improves cognition and modulates beta amyloid in early AD. *Neurology*. 2008; 70:440–448. [PubMed: 17942819]
- Risner ME, Saunders AM, Altman JF, Ormandy GC, Craft S, Foley IM, Zvartau Hind ME, Hosford DA, Roses AD. Efficacy of rosiglitazone in a genetically defined population with mild to moderate Alzheimer's disease. *Pharmacogenomics J*. 2006; 6:246–254. [PubMed: 16446752]
- Rivera EJ, Goldin A, Fulmer N, Tavares R, Wands JR, de la Monte SM. Insulin and insulin like growth factor expression and function deteriorate with progression of Alzheimer's disease: link to brain reductions in acetylcholine. *J Alzheimers Dis*. 2005; 8:247–268. [PubMed: 16340083]
- Rowe WB, Blalock EM, Chen KC, Kadish I, Wang D, Barrett JE, Thibault O, Porter NM, Rose GM, Landfield PW. Hippocampal expression analyses reveal selective association of immediate early, neuroenergetic, and myelinogenic pathways with cognitive impairment in aged rats. *J Neurosci*. 2007; 27:3098–3110. [PubMed: 17376971]
- Ryan CM, Freed MI, Rood JA, Cobitz AR, Waterhouse BR, Strachan MW. Improving metabolic control leads to better working memory in adults with type 2 diabetes. *Diabetes Care*. 2006; 29:345–351. [PubMed: 16443885]
- Ryan CM, Geckle M. Why is learning and memory dysfunction in Type 2 diabetes limited to older adults? *Diabetes Metab Res Rev*. 2000; 16:308–315. [PubMed: 11025555]
- Sapolsky RM. Glucocorticoids, stress, and their adverse neurological effects: relevance to aging. *Experimental gerontology*. 1999; 34:721–732. [PubMed: 10579633]
- Scott LJ, Mohlke KL, Bonnycastle LL, Willer CJ, Li Y, Duren WL, Erdos MR, Stringham HM, Chines PS, Jackson AU, Prokunina Olsson L, Ding CJ, Swift AJ, Narisu N, Hu T, Pruim R, Xiao R, Li XY, Conneely KN, Riebow NL, Sprau AG, Tong M, White PP, Hetrick KN, Barnhart MW, Bark CW, Goldstein JL, Watkins L, Xiang F, Saramies J, Buchanan TA, Watanabe RM, Valle TT, Kinnunen L, Abecasis GR, Pugh EW, Doheny KF, Bergman RN, Tuomilehto J, Collins FS, Boehnke M. A genome wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. *Science*. 2007; 316:1341–1345. [PubMed: 17463248]
- Searcy JL, Phelps JT, Pancani T, Kadish I, Popovic J, Anderson KL, Beckett TL, Murphy MP, Chen KC, Blalock EM, Landfield PW, Porter NM, Thibault O. Long term pioglitazone treatment improves learning and attenuates pathological markers in a mouse model of Alzheimer's disease. *J Alzheimers Dis*. 2012; 30:943–961. [PubMed: 22495349]
- Seckl JR, Walker BR. 11beta hydroxysteroid dehydrogenase type 1 as a modulator of glucocorticoid action: from metabolism to memory. *Trends in endocrinology and metabolism: TEM*. 2004; 15:418–424. [PubMed: 15519888]
- Sharma M, Gupta YK. Intracerebroventricular injection of streptozotocin in rats produces both oxidative stress in the brain and cognitive impairment. *Life Sci*. 2001; 68:1021–1029. [PubMed: 11212865]
- Simpkins JW, Singh M, Brock C, Etgen AM. Neuroprotection and estrogen receptors. *Neuroendocrinology*. 2012; 96:119–130. [PubMed: 22538356]
- Simpson IA, Appel NM, Hokari M, Oki J, Holman GD, Maher F, Koehler Stec EM, Vannucci SJ, Smith QR. Blood brain barrier glucose transporter: effects of hypo and hyperglycemia revisited. *J Neurochem*. 1999; 72:238–247. [PubMed: 9886075]
- Skeberdis VA, Lan J, Zheng X, Zukin RS, Bennett MV. Insulin promotes rapid delivery of N methyl D aspartate receptors to the cell surface by exocytosis. *Proc Natl Acad Sci U S A*. 2001; 98:3561–3566. [PubMed: 11248117]
- Steen E, Terry BM, Rivera EJ, Cannon JL, Neely TR, Tavares R, Xu XJ, Wands JR, de la Monte SM. Impaired insulin and insulin like growth factor expression and signaling mechanisms in Alzheimer's disease is this type 3 diabetes? *J Alzheimers Dis*. 2005; 7:63–80. [PubMed: 15750215]
- Stocker M. Ca(2+) activated K+ channels: molecular determinants and function of the SK family. *Nat Rev Neurosci*. 2004; 5:758–770. [PubMed: 15378036]
- Storlien LH, James DE, Burleigh KM, Chisholm DJ, Kraegen EW. Fat feeding causes widespread in vivo insulin resistance, decreased energy expenditure, and obesity in rats. *Am J Physiol*. 1986; 251:E576–583. [PubMed: 3535532]

- Stranahan AM, Arumugam TV, Cutler RG, Lee K, Egan JM, Mattson MP. Diabetes impairs hippocampal function through glucocorticoid mediated effects on new and mature neurons. *Nat Neurosci.* 2008a; 11:309–317. [PubMed: 18278039]
- Stranahan AM, Lee K, Pistell PJ, Nelson CM, Readal N, Miller MG, Spangler EL, Ingram DK, Mattson MP. Accelerated cognitive aging in diabetic rats is prevented by lowering corticosterone levels. *Neurobiology of learning and memory.* 2008b; 90:479–483. [PubMed: 18579418]
- Stranahan AM, Norman ED, Lee K, Cutler RG, Telljohann RS, Egan JM, Mattson MP. Diet induced insulin resistance impairs hippocampal synaptic plasticity and cognition in middle aged rats. *Hippocampus.* 2008c; 18:1085–1088. [PubMed: 18651634]
- Sundararajan S, Jiang Q, Heneka M, Landreth G. PPARgamma as a therapeutic target in central nervous system diseases. *Neurochem Int.* 2006; 49:136–144. [PubMed: 16766086]
- Swerdlow RH. PET sheds light on Alzheimer's disease genetic risk. *Proc Natl Acad Sci U S A.* 2007; 104:18881–18882. [PubMed: 18025455]
- Takayama M, Hirose N, Arai Y, Gondo Y, Shimizu K, Ebihara Y, Yamamura K, Nakazawa S, Inagaki H, Masui Y, Kitagawa K. Morbidity of Tokyo area centenarians and its relationship to functional status. *J Gerontol A Biol Sci Med Sci.* 2007; 62:774–782. [PubMed: 17634326]
- Talbot K, Wang HY, Kazi H, Han LY, Bakshi KP, Stucky A, Fuino RL, Kawaguchi KR, Samoyedny AJ, Wilson RS, Arvanitakis Z, Schneider JA, Wolf BA, Bennett DA, Trojanowski JQ, Arnold SE. Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF 1 resistance, IRS 1 dysregulation, and cognitive decline. *J Clin Invest.* 2012; 122:1316–1338. [PubMed: 22476197]
- Thibault O, Gant JC, Landfield PW. Expansion of the calcium hypothesis of brain aging and Alzheimer's disease: minding the store. *Aging Cell.* 2007; 6:307–317. [PubMed: 17465978]
- Thibault O, Hadley R, Landfield PW. Elevated postsynaptic [Ca²⁺]_i and L type calcium channel activity in aged hippocampal neurons: relationship to impaired synaptic plasticity. *J Neurosci.* 2001; 21:9744–9756. [PubMed: 11739583]
- Thibault O, Landfield PW. Increase in single L type calcium channels in hippocampal neurons during aging. *Science.* 1996; 272:1017–1020. [PubMed: 8638124]
- Thibault O, Porter NM, Chen KC, Blalock EM, Kaminker PG, Clodfelter GV, Brewer LD, Landfield PW. Calcium dysregulation in neuronal aging and Alzheimer's disease: history and new directions. *Cell Calcium.* 1998; 24:417–433. [PubMed: 10091010]
- To AW, Ribe EM, Chuang TT, Schroeder JE, Lovestone S. The epsilon3 and epsilon4 alleles of human APOE differentially affect tau phosphorylation in hyperinsulinemic and pioglitazone treated mice. *PLoS ONE.* 2011; 6:e16991. [PubMed: 21347323]
- Toescu EC, Verkhatsky A. The importance of being subtle: small changes in calcium homeostasis control cognitive decline in normal aging. *Aging Cell.* 2007; 6:267–273. [PubMed: 17517038]
- Tombaugh GC, Rowe WB, Rose GM. The slow afterhyperpolarization in hippocampal CA1 neurons covaries with spatial learning ability in aged Fisher 344 rats. *J Neurosci.* 2005; 25:2609–2616. [PubMed: 15758171]
- van der Heide LP, Kamal A, Artola A, Gispen WH, Ramakers GM. Insulin modulates hippocampal activity dependent synaptic plasticity in a N methyl d aspartate receptor and phosphatidyl inositol 3 kinase dependent manner. *J Neurochem.* 2005; 94:1158–1166. [PubMed: 16092951]
- van der Heide LP, Ramakers GM, Smidt MP. Insulin signaling in the central nervous system: learning to survive. *Prog Neurobiol.* 2006; 79:205–221. [PubMed: 16916571]
- Verkhatsky A, Fernyhough P. Mitochondrial malfunction and Ca²⁺ dyshomeostasis drive neuronal pathology in diabetes. *Cell calcium.* 2008; 44:112–122. [PubMed: 18191198]
- Watson GS, Cholerton BA, Reger MA, Baker LD, Plymate SR, Asthana S, Fishel MA, Kulstad JJ, Green PS, Cook DG, Kahn SE, Keeling ML, Craft S. Preserved cognition in patients with early Alzheimer disease and amnesic mild cognitive impairment during treatment with rosiglitazone: a preliminary study. *Am J Geriatr Psychiatry.* 2005; 13:950–958. [PubMed: 16286438]
- Watson GS, Craft S. The role of insulin resistance in the pathogenesis of Alzheimer's disease: implications for treatment. *CNS Drugs.* 2003; 17:27–45. [PubMed: 12467491]
- Watson GS, Craft S. Modulation of memory by insulin and glucose: neuropsychological observations in Alzheimer's disease. *Eur J Pharmacol.* 2004; 490:97–113. [PubMed: 15094077]

- Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. *The Journal of clinical investigation*. 2003; 112:1796–1808. [PubMed: 14679176]
- Whitmer RA, Gunderson EP, Quesenberry CP Jr, Zhou J, Yaffe K. Body mass index in midlife and risk of Alzheimer disease and vascular dementia. *Current Alzheimer research*. 2007; 4:103–109. [PubMed: 17430231]
- Whitmer RA, Gustafson DR, Barrett Connor E, Haan MN, Gunderson EP, Yaffe K. Central obesity and increased risk of dementia more than three decades later. *Neurology*. 2008
- Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care*. 2004; 27:1047–1053. [PubMed: 15111519]
- Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, Sole J, Nichols A, Ross JS, Tartaglia LA, Chen H. Chronic inflammation in fat plays a crucial role in the development of obesity related insulin resistance. *The Journal of clinical investigation*. 2003; 112:1821–1830. [PubMed: 14679177]
- Yaffe K, Blackwell T, Kanaya AM, Davidowitz N, Barrett Connor E, Krueger K. Diabetes, impaired fasting glucose, and development of cognitive impairment in older women. *Neurology*. 2004; 63:658–663. [PubMed: 15326238]
- Yaffe K, Falvey C, Hamilton N, Schwartz AV, Simonsick EM, Satterfield S, Cauley JA, Rosano C, Launer LJ, Strotmeyer ES, Harris TB. Diabetes, glucose control, and 9 year cognitive decline among older adults without dementia. *Arch Neurol*. 2012; 69:1170–1175. [PubMed: 22710333]
- Yao J, Hamilton RT, Cadenas E, Brinton RD. Decline in mitochondrial bioenergetics and shift to ketogenic profile in brain during reproductive senescence. *Biochim Biophys Acta*. 2010; 1800:1121–1126. [PubMed: 20538040]
- Yu C, Chen Y, Cline GW, Zhang D, Zong H, Wang Y, Bergeron R, Kim JK, Cushman SW, Cooney GJ, Atcheson B, White MF, Kraegen EW, Shulman GI. Mechanism by which fatty acids inhibit insulin activation of insulin receptor substrate 1 (IRS 1) associated phosphatidylinositol 3 kinase activity in muscle. *J Biol Chem*. 2002; 277:50230–50236. [PubMed: 12006582]
- Zhao W, Chen H, Xu H, Moore E, Meiri N, Quon MJ, Alkon DL. Brain insulin receptors and spatial memory. Correlated changes in gene expression, tyrosine phosphorylation, and signaling molecules in the hippocampus of water maze trained rats. *J Biol Chem*. 1999; 274:34893–34902. [PubMed: 10574963]
- Zhao WQ, Alkon DL. Role of insulin and insulin receptor in learning and memory. *Molecular and cellular endocrinology*. 2001; 177:125–134. [PubMed: 11377828]

Figure 1.

Twenty-four hour pioglitazone (PIO) treatment reduces intracellular NMDA-induced $[\text{Ca}^{2+}]$. (a) shows representative Fura-2-loaded hippocampal neurons used for ratiometric analyses on intracellular Ca^{2+} concentrations taken before (baseline), and during (peak) NMDA exposure (300 μM , 5 s) in control-treated (CTRL) and PIO-treated cells. (b) shows group data in control-treated (CTRL) and PIO-treated cells imaged before, during (thick horizontal bar) and after NMDA exposure (* $p < 0.05$; Tukey's *post-hoc* test). Used with permission from: © 2009 The Authors. Journal Compilation © 2009 International Society for Neurochemistry.

Figure 2.

Twenty-four hour pioglitazone (PIO) reduces NMDAR-mediated currents. (a) shows representative current traces in response to a 500 ms, 300 μ M NMDA pulse (horizontal bar). Cultures were treated either with DMSO (0.1%) or PIO (10 μ M) alone or in combination with the agonists. (b) shows corresponding mean group current density data (means $\pm$ SEM) recorded under these treatment conditions ($n = 6-34$). PIO significantly reduced NMDAR-mediated current density (* $p < 0.05$; ANOVA). The PIO effect on NMDAR-mediated current was prevented when the selective PPAR- antagonist T0070907 (TIO) was added in combination with PIO for 24 h. Used with permission from: © 2009 The Authors. Journal Compilation © 2009 International Society for Neurochemistry.

Figure 3.

Measures of the Ca^{2+} -dependent slow afterhyperpolarization (sAHP). (A) Representative examples of AHPs recorded in CA1 pyramidal cells from young (left) and aged (right) animals fed either control (CTRL) or pioglitazone-enriched (PIO) diet. Both amplitude (B) and duration (C) of the sAHP were significantly enhanced in the aged group. In aged animals, however, long-term PIO treatment significantly reduced the sAHP (red traces in A). * indicates significant aging and PIO effects (two-way ANOVA, $p < 0.05$). Data represent mean $\pm$ SEM in 12–21 recorded neurons from 6–7 animals per group. From Blalock et al., 2010.

Figure 4.

High frequency induced long-term potentiation. Normalized EPSP slopes measured in control (CTRL - white circles) and pioglitazone (PIO - black circles) fed animals during baseline and following a 1 s 100 Hz stimulation burst. All measures taken after LTP induction were significantly greater in the PIO group. Inserts represent EPSP traces taken before LTP induction (black), and in the last 5 minutes of recording (red). Data represent Mean $\pm$ SEM, ** $p < 0.01$, RM-ANOVA. With permission from Searcy et al., 2012.

Figure 5. The acute effects of insulin on the slow afterhyperpolarization (sAHP). (A and B) Degree of insulin-mediated AHP reduction, and hence, insulin sensitivity in control diet (CD) and high-fat diet (HFD) animals, respectively. Although insulin reduced the sAHP in both age groups, the degree of inhibition appeared to be greater in older animals on CD (A). HFD was able to reduce insulin sensitivity in older animals (B). * indicate significant difference at the level of $p < 0.05$. Used with permission from: © 2013 The Authors. Elsevier.