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Review

Hippocampal calcium dysregulation at the nexus of diabetes and brain aging

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ABSTRACT

Recently it has become clear that conditions of insulin resistance/metabolic syndrome, obesity and diabetes, are linked with moderate cognitive impairment in normal aging and elevated risk of Alzheimer's disease. It appears that a common feature of these conditions is impaired insulin signaling, affecting the brain as well as 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 diabetes induces Ca^{2+} dysregulation in neurons. Because brain aging is associated with substantial Ca^{2+} dyshomeostasis, it has been proposed that impaired 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. The drugs appear able to reduce the age-dependent increase in Ca^{2+} transients and the Ca^{2+} -sensitive afterhyperpolarization. Thus, while additional testing is needed, the results to date are consistent with the view that strategies that enhance insulin signaling can counteract the effect of aging on Ca^{2+} dysregulation.

Contents

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1. 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 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 as 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 (Gispen 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, 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. 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 lifestyle 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 phosphotidyl inositol 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 >6000 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 et al., 2006; 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., 2013; 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 Aβ clearance or degradation, weak synaptic communication, hyperphosphorylation of microtubule-associated proteins (Tau), altered Ca^{2+} regulation, elevated glucocorticoids and increased 11beta hydroxysteroid dehydrogenase