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Review

Neuroprotective effects of leptin in the context of obesity and metabolic disorders

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ABSTRACT

As the population of the world ages, the prevalence of neurodegenerative disease continues to rise, accompanied by increases in disease burden related to obesity and metabolic disorders. Thus, it will be essential to develop tools for preventing and slowing the progression of these major disease entities. Epidemiologic studies have shown strong associations between obesity, metabolic dysfunction, and neurodegeneration, while animal models have provided insights into the complex relationships between these conditions. Experimentally, the fat-derived hormone leptin has been shown to act as a neuroprotective agent in various animal models of dementia, toxic insults, ischemia/reperfusion, and other neurodegenerative processes. Specifically, leptin minimizes neuronal damage induced by neurotoxins and pro-apoptotic conditions. Leptin has also demonstrated considerable promise in animal models of obesity and metabolic disorders via modulation of glucose homeostasis and energy intake. However, since obesity is known to induce leptin resistance, we hypothesize that resistance to the neuroprotective effects of leptin contributes to the pathogenesis of obesity-associated neurodegenerative diseases. This review aims to explore the literature pertinent to the role of leptin in the protection of neurons from the toxic effects of aging, obesity and metabolic disorders, to investigate the physiological state of leptin resistance and its causes, and to consider how leptin might be employed therapeutically in the prevention and treatment of neurodegenerative disease.

Contents

Introduction

As the general population progressively ages, the prevalence of obesity, metabolic disease, and neurodegenerative disease continues to rise. Neurodegenerative diseases belong to a class of diseases that appears to be associated with age and obesity. Specifically, Parkinson's disease and

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Alzheimer's disease together have a prevalence of about three percent at age 65, but by age 95 the prevalence rises to 55% (Alves et al., 2008; Wang and Ding, 2008). Concurrent with the population-wide rise in neurodegenerative disease is an increased prevalence of obesity, which appears to be etiologically associated with neurodegeneration. The World Health Organization estimates that in 2008 35% of adults aged 20 and above were overweight, while 11% of this population was obese (WHO, 2013). Obesity is associated with a wide array of deleterious consequences, including cardiovascular disease, type 2 diabetes, dyslipidemia, sleep apnea, liver disease, obesity-related cancers, osteoarthritis, and psychological problems (Dixon, 2010). There is also growing evidence to suggest that obesity is a risk factor for the development of dementia.

A potential therapeutic option supported by basic science research for all of these inter-related pathological states is the adipokine leptin. Leptin is an endogenous hormone produced most notably by adipose tissue in direct proportion to fat mass (Klein et al., 1996). Leptin has been shown to promote neuronal survival in pro-apoptotic environments and also to attenuate neuronal damage in animal models of neurodegenerative disease. Leptin has also been implicated for its mechanistic importance and potential therapeutic use in various obesity-associated metabolic diseases, including lipodystrophy and type 2 diabetes. Although obesity is associated with elevated leptin levels, it also confers a state of leptin resistance, such that the neuroprotective effects of leptin are likely to be attenuated. Given that obesity is both a common predating symptom and risk factor for metabolic and neurodegenerative diseases, efforts to elucidate the therapeutic potential of leptin for these two types of disease require a thorough understanding of the mechanism of leptin signaling within both the endocrine and nervous systems.

Obesity is a condition in which an excess of fat mass accumulates to the point that it has a negative impact on the health of an individual. A meta-analysis performed by Gorospe and Dave suggested that BMI may be an independent risk factor for dementia after controlling for such other well-known risk factors such as age, gender, smoking, comorbidities, APOE-ε4 level (Gorospe and Dave, 2007). In fact, strong evidence suggests that mid-life obesity is a risk factor for later-life development of dementia (Hassing et al., 2009; Kivipelto et al., 2005; Whitmer et al., 2005, 2008; Xu et al., 2011), specifically in the form of Parkinson's disease (Abbott et al., 2002), Alzheimer's disease (Hassing et al., 2009; Kivipelto et al., 2005; Whitmer et al., 2007; Xu et al., 2011) and vascular dementia (Hassing et al., 2009; Whitmer et al., 2007; Xu et al., 2011).

Not only is obesity a risk factor for the development of dementia later in life, but it has also been found to be associated with lower brain volumes (Ward et al., 2005), decreased gray matter density (Pannacciulli et al., 2006), and lower cognitive function in middle-age individuals (Elias et al., 2003, 2005). Elias et al. found that obesity was related to cognitive deficits in men – but not women – who participated in the Framingham Heart Study after controlling for other risk factors, including age, education, occupation, smoking behavior, and diabetes mellitus (Elias et al., 2003, 2005). Wolf et al. found that both men and women in the Framingham Offspring Cohort with the highest proportion of central obesity as measured by Waist–Hip ratio had significantly lower scores in cognitive testing (Wolf et al., 2007).

Alzheimer's disease and associated metabolic dysfunction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder resulting in neurological deficits including memory loss and diminished cognitive function. Using 2010 United States Census data, Hebert et al. estimated that 4.7 million Americans aged 65 or older suffered from the disease, making it the most common neurological condition in the United States (Hebert et al., 2013). By these same statistics, prevalence of AD in the US is expected to increase to 13.8 million by 2050, with a prevalence of over 7 million individuals projected in the above-85 age bracket. Current treatment modalities for the disease have been shown to be only marginally effective, demonstrating benefit in managing symptoms and slowing of cognitive decline but not in global disease progression (Rountree et al., 2009).

Significant evidence points toward an association between risk of development of Alzheimer's disease and such factors as excess body weight at midlife, sedentary lifestyle, and a fat-rich, sugar-rich diet (Cai et al., 2012; Farris et al., 2003; Mayeux and Stern, 2012; Simons et al., 2006). Such a high-fat diet is thought to modulate changes to hippocampal function via glucotoxicity (the toxic effects of increased glucose availability) or disrupted insulin signaling, suggesting a potential connection between obesity and AD (Cai et al., 2012). Patients with diabetes have been found to have two-fold greater risk of developing AD than patients without the disease, while patients with type 2 Diabetes and the ApoE4 allele are at a five-fold greater risk of developing AD than their counterparts without either of those conditions (Ott et al., 1999; Peila et al., 2002). The association between hyperglycemia and development of AD is strong, as glucose administration is directly correlated to the cleavage of tau – a microtubule-stabilizing protein found abundantly in the axons of neurons of the CNS – that is widely accepted as a predecessor of AD pathology (Kim et al., 2009). Glucose levels are also positively correlated with apoptosis in the *db*/*db* mouse, which, due to a premature stop codon mutation that renders the leptin receptor (Ob-Rb) non-functional, exhibits an obese phenotype and characteristics that qualify it as an effective model for type 2 diabetes (Chen et al., 1996; Kim et al., 2009). According to a 2004 review of the Mayo Clinic Alzheimer Disease Patient Registry records, more than 80% of the AD patients were affected with type 2 DM or impaired fasting glucose (Janson et al., 2004). Recent studies also indicate a connection between low-grade chronic inflammation associated with Metabolic Syndrome and cognitive impairment preceding AD (Misiak et al., 2012). Together these findings suggest a connection between AD and sequelae associated with metabolic dysfunction.

Parkinson's disease and associated metabolic dysfunction

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease. Epidemiological studies using 2010 US census estimates have estimated that 630,000 Americans were living with diagnosed PD in 2010, with a prevalence of 1–2% of the population above the age of 65 and 4–5% above the age of 85 (Kowal et al., 2013). The clinical presentation of PD typically consists of bradykinesia, resting tremor, rigidity, and gait instability (Cai et al., 2012). Parkinson's disease is primarily a disorder of motor function characterized by significant loss of dopaminergic neurons in the pars-compacta of the substantia nigra by an unknown mechanism. The low levels of expression of brain-derived neurotrophic factor (BDNF), a critical neuronal growth factor found in the central and peripheral nervous system (Mogi et al., 1999; Parain et al., 1999), in the substantia nigra and the relative lack of dopaminergic neurons in PD patients and mouse models suggest the critical role played by BDNF in normal development of those neurons (Baquet et al., 2005; Kohno et al., 2004). While treatments for Parkinson's disease are more advanced and effective than treatments for Alzheimer's, patients with PD still consistently progress to end-stage disease.

Paradoxically, while midlife adiposity and consumption of a carbohydrate-rich diet have been found to predict subsequent onset of Parkinson's disease later in life (Abbott et al., 2002, 2003), metabolic dysfunction in Parkinson's patients is generally associated with weight loss upon disease onset, as well as evidence of alteration in glucose homeostasis and insulin signaling. Although PD patients do not exhibit reduced energy intake, they typically lose significant weight from the illness both before and after diagnosis and present lower BMI on average than their age-matched normal controls (Abbott et al., 1992; Beyer et al., 1995; Chen et al., 2003). In PD patients who experience unintentional weight loss, circulating leptin levels have been found to be lower than in weight-stable PD patients, with lowered leptin levels

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