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Invited critical review

Leptin in Alzheimer's disease

Magalhães CA [a], Carvalho MG [a], Sousa LP [a], Caramelli P [b], Gomes KB [a,*]

[a] Departamento de Análises Clínicas e Toxicológicas, Faculdade de Farmácia, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil.
[b] Departamento de Clínica Médica, Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil.

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ABSTRACT

Alzheimer's disease (AD) is the most common cause of progressive dementia in the elderly population. AD is histologically characterized by accumulation of amyloid-β protein (Aβ) on extracellular plaques and deposition of hyperphosphorylated tau protein in intracellular neurofibrillary tangles. Several studies have shown that obesity may precede dementia and that lifestyle factors play a critical role in the onset of AD. Furthermore, accumulating evidence indicates that obesity is an independent risk factor for developing AD. In this scenario, the understanding of the role of adipose tissue in brain health is essential to clarify the establishment of demential processes. The objective of this work was to review studies regarding leptin, an anorexigenic peptide hormone synthesized in adipocytes, in the context of dementia. Some authors proposed that leptin evaluation might be a better predictor of dementia than traditional anthropometric measures. Leptin, once established as a biomarker, could enhance the understanding of late-onset AD risk over the life course, as well as the clinical progression of prodromal state to manifested AD. Other studies have proposed that leptin presents neuroprotective activities, which could be explained by inhibiting the amyloidogenic process, reducing the levels of tau protein phosphorylation and improving the cognitive function.

Contents

1. Introduction

Alzheimer's disease (AD) is the most common cause of progressive dementia in the elderly population [1–3]. This chronic neurodegenerative disorder leads to progressive disturbances of cognitive functions including memory, judgment, decision-making, orientation to physical surroundings and language [4]. AD is histologically characterized by the accumulation of amyloid-β protein (Aβ) on extracellular plaques and deposition of hyperphosphorylated tau protein in intracellular neurofibrillary tangles [5–8]. According to Alzheimer's Association (2015), the disease prevalence is one case in nine elderly with 65 years or more [1].

Recent studies suggest that lifestyle factors, including nutritional behaviors and stress, play a critical role in the onset of dementia and those individuals with AD present a generalized metabolic disorder [9]. The relationship between nutritional behavior and AD includes the role of obesity, hypertension, dyslipidemia and elevated glucose levels in the disease development or progression. Some clinical studies support the association between metabolic syndrome and the onset of AD [10,11]. In agreement with this hypothesis, some studies have suggested that

* Corresponding author at: Faculdade de Farmácia, Universidade Federal de Minas Gerais, Avenida Antônio Carlos, 6627, Pampulha, Belo Horizonte, Minas Gerais, Brazil.
E-mail address: karinabgb@gmail.com (G. KB).

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overweight or obesity in middle age is considered an important risk factor for later development of AD [12,13]. Additionally, a consistent observation is that individuals with AD, despite unchanged eating habits, begin to lose weight some years before the onset of clinical symptoms, suggesting a relation between adipose tissue metabolism and AD [14–16]. Prospective studies have showed that obesity precedes dementia and adipokines had been reported in epidemiologic studies associated with cognitive decline [17].

Gustafson (2010) have suggested that clarifying the role of adipose tissue in health of the brain is essential to a complete understanding of demential processes [18].

The Gustafson et al. (2012) also demonstrated that high mid-life central adiposity might increase the risk for dementia after 32 years [19].

Accumulating evidence indicates that obesity is an independent risk factor for developing Alzheimer disease (AD). Zeki et al. (2013) proposed that leptin, an adipokine, might be a better predictor of dementia/mild cognitive impairment (MCI) than traditional anthropometric measures [20]. They observed association between higher serum leptin and lower frequency of dementia/MCI in women with normal body mass index than overweight or obese women. Koga et al. (2014) verified that diet-induced obesity enhanced Aβ and tau induced-pathology in wild-type mice hippocampus [21]. They demonstrated that persistent obesity from early life induces tau phosphorylation in the hippocampus accompanied by enhanced astroglial leptin receptor (LEPR) expression that might accelerate pathological processes in neurodegenerative disorders.

The aim of this work was to elaborate a narrative review regarding the role of leptin in the context of dementia. The gathered data suggest that variations in the leptin levels can be a risk factor associated with the occurrence of AD.

2. Material and methods

For this narrative review, a search was done in Pubmed, Cochrane, Science Direct, Scopus and Web of Science database with the terms “dementia”, “Alzheimer's disease”, “adipokines”, “leptin” and studies reporting on “associations between Alzheimer's disease and leptin”, with no date or type of study restrictions. We included in this review 69 studies published between 1998 and 2015, in English and Portuguese languages.

3. Leptin

The adipose tissue is responsible for production of regulatory molecules, which may be assorted in a group — the adipokines. The word adipokine or adipocytokine means adipose cell in movement. Adipokines have autocrine, paracrine, and endocrine mechanisms of action and many adipokines affect processes in both the peripheral and central nervous system (CNS) [22,23]. Adipokine release can be dysregulated in both obesity and ageing, possibly due to impaired function. The term “adiposopathy” has been used to describe dysregulated adipose tissue and adipokine levels with excessive hypertrophy of adipocytes [22].

Leptin is an adipokine composed of 167 amino acids, first related in 1994 by Zhang et al. [24]. The name leptin (Lep) is derived from the Greek *leptos*, which means thin. The human leptin is encoded by the LEP gene (also called obese, OB) on chromosome 7q32; its gene spans approximately 20 Kb and contains 3 exons [25].

Leptin is an anorexigenic peptide hormone synthesized and secreted from adipocytes, mainly by white adipose tissue and in very small amounts by brown adipose tissue. This hormone is actively transported across the blood–brain barrier and acts on hypothalamic modulation of feeding behavior and energy expenditure [26,27]. Leptin is also synthetized in other tissues, including placenta, ovaries, skeletal muscle and stomach [28].

Circulating concentrations of leptin exhibit pulsatility and circadian rhythmicity. Unlike other inflammatory mediators, leptin is readily detectable in circulation under normal conditions and fluctuates to regulate the energy status of the body [29]. The levels of plasma leptin vary directly with the body mass index and percentage of body fat. Metabolic hormones, sex, and body energy requirements influence its plasma concentration. Leptin has historically been associated with obesity, since defects in the leptin signaling pathway result in obesity in animal models. Only a few obese humans have been identified with mutations in the leptin gene or in the leptin receptor, however, most cases of obesity in humans are associated with high leptin levels. Thus, human obesity may represent a state of leptin resistance. The fluctuations in peripheral leptin concentrations influence the activity of the hypothalamic–pituitary–ovarian and hypothalamic–pituitary–adrenal axes, indicating that leptin may be a modulator of reproduction, stress-related endocrine function and behavior [30].

Leptin receptors (LEPRs) are present in both hypothalamic and extrahypothalamic neurons, including neurons of the hippocampus and cerebral cortex, brain stem and cerebellum [31,32]. Six different isoforms from the leptin receptor gene are synthesized: Ob-Ra, Ob-Rb, Ob-Rc, Ob-Rd, Ob-Re and Ob-Rf. They are generally classified into the short (ObRa, c, d, and f), long (ObRb) and soluble (ObRe) forms [33]. The long form is responsible for signaling induced by ligand binding and eliciting an array of subsequent intracellular signaling cascades [33]. The short forms are less involved in leptin activated intracellular signaling. They appear important in mediating the transfer of leptin from the periphery through the blood–brain barrier. It has been demonstrated that leptin is able to bind in megalin-LRP2, a multi-ligand receptor that is expressed in choroid plexus epithelial cells (Fig. 1) [33].

LEPR activates several downstream molecules involved in pathways related to cell survival and metabolism such as STAT3, PI3K, AMPK, AKT, SIRTUIN1 and GSK3b. These pathways form a network that is involved in leptin physiological response [34,35].

4. Alzheimer's disease and leptin

Leptin is the most studied adipokine associated with brain structure and function, and has several effects on the brain in relation to cognition and ageing (Table 1). Recent studies indicate a remarkable effect of the leptin on hippocampal development and function, mainly learning and memory processes. Leptin dysfunction has recently been linked to AD [36,37]. Farr et al. (2006) showed that leptin was able to improve memory processing in mice model, which normally develop elevated amyloid-β and memory deficits in advancing age [38]. Warren et al. (2012) suggested that leptin was associated with higher Montreal Cognitive Assessment (MoCA) total scores and delayed recall domain score for white men [39].

Leptin acts in the hippocampus to promote hippocampal synaptic plasticity, including enhancement of neuronal morphology, and increases the neurogenesis and synaptic transmission. Studies using animal models of ageing and AD have shown that achieving energy balance in adipose tissue, through feeding and exercises can improve cognitive function and prevent an age-related decline in learning [40]. In the same sense, Folch et al. (2012) have proposed that leptin presents neuroprotective activities, which could be explained by inhibiting the amyloidogenic process, reducing the phosphorylation levels of tau protein and improving the cognitive function [34].

Lieb et al. (2009) provided evidence for a lower incidence of AD in nonobese individuals with higher leptin levels [41]. Bigalke et al. (2011) have found that AD patients had significantly decreased plasma levels of leptin compared with healthy controls [36]. However, Theodoropoulou et al. (2012) found no difference in leptin level between patients with AD and controls [37].

Data obtained by Hazzouri et al. (2013) corroborated the evidence that obesity may interfere with the neuroprotective effect of leptin on the brain, possibly by leptin resistance [42]. Leptin resistance may result