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Minireview

The role of leptin in the sporadic form of Alzheimer's disease. Interactions with the adipokines amylin, ghrelin and the pituitary hormone prolactin

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ABSTRACT

Leptin (Lep) is emerging as a pivotal molecule involved in both the early events and the terminal phases of Alzheimer's disease (AD). In the canonical pathway, Lep acts as an anorexigenic factor via its effects on hypothalamic nucleus. However, additional functions of Lep in the hippocampus and cortex have been unravelled in recent years. Early events in the sporadic form of AD likely involve cellular level alterations which can have an effect on food intake and metabolism. Thus, AD can be conceivably interpreted as a multiorgan pathology that not only results in a dramatic neuronal loss in brain areas such as the hippocampus and the cortex (ultimately leading to a significant cognitive impairment) but as a disease which also affects body-weight homeostasis. According to this view, body-weight control disruptions are to be expected in both the early- and late-stage AD, concomitant with changes in serum Lep content, alterations in Lep transport across the blood–brain barrier (BBB) and Lep receptor-related signalling abnormalities. Lep is a member of the adipokine family of molecules, while the Lep receptor belongs to the class I cytokine receptors. Since cellular response to adipokine signalling can be either potentiated or diminished as a result of specific ligand–receptor interactions, Lep interactions with other members of the adipokine family including amylin, ghrelin and hormones such as prolactin require further investigation. In this review, we provide a general perspective on the functions of Lep in the brain, with a particular focus on the sporadic AD.

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1. Introduction

Alzheimer's disease is one of the most common causes of senile dementia and it is estimated that by 2050, the number of cases will rise to 110 million [1,2]. The vast majority of patients suffer from the sporadic AD, with only a small subset of the population presenting with the familial form as a result of mutations in amyloid precursor protein (APP) Presenilin 1 or Presenilin 2 genes [3,4].

AD progression is associated with the formation of senile β-amyloid (Aβ) plaques and accumulations of hyperphosphorylated Tau proteins called neurofibrillary tangles in the brain [5,6]. Clinically, AD is characterized by a progressive loss of cognitive abilities as a result of severe hippocampal neurodegeneration, with the biggest impact on memory and learning faculties [7,8]. Aβ peptides are generated by a specific proteolytic cleavage of the APP. In this amyloidogenic pathway, the β- and γ-Secretases cleave APP at the N- and C-termini of the Aβ, respectively. The relationship between the aberrant APP processing and Aβ generation caused the formulation of the widely accepted "amyloid cascade hypothesis". It states that mutations in APP (or other genes) lead to an increase in Aβ which, when accumulated, leads to disease [9,10].

Apart from the Aβ itself, a host of other factors contributing to AD pathology have been identified: oxidative stress and ROS generation, alterations in glucose metabolism, deregulation of Ca^{2+} signalling, deregulation of glial cell activity, alterations in nutritional behaviour, metabolic syndrome and obesity, hypertension and type 2 diabetes mellitus (T2DM) [11–19]. Thus, it is difficult to point out a single pathogenic mechanism leading to the onset and progression of this devastating disease. It has been suspected for many years that AD may in fact be a multifactorial metabolic disorder influenced by several risk factors such as hypertension, diabetes, hypercholesterolaemia, neuroinflammation and hypoxia, among others [13–15].

In the next sections we discuss some of the metabolic aspects of AD, with a special emphasis on adipokines in general, and leptin in particular.

2. Lifestyle and AD

As a means to slow down the onset of disease symptoms, researchers have turned their attention to the relationship between lifestyle and AD [20]. Lifestyle-related diseases are potentially preventable, and their incidence can be decreased with adequate changes in diet, amount of physical activity and modification of the environment. The common feature at the core of most lifestyle diseases is obesity, and accumulating evidence indicates that obesity is an independent risk factor for developing AD. Obesity is a pandemic and a serious global health concern. Obesity is also a risk factor for multiple conditions and contributes to multi-morbidities, resulting in increased healthcare costs and millions of deaths each year [21]. Obesity has been associated with changes in brain structure, cognitive deficits, dementia and AD. In agreement with this, high-fat diet (HFD)-induced obesity also causes a variety of health disorders including cognitive decline in experimental animal models [22]. There is a well-established link between human obesity and cognitive decline [23]. Specific brain functions related to the hippocampus may be particularly vulnerable as evidenced in a large number of studies in rodents linking high-caloric diets with decreased contextual and spatial memory [24–29]. Significantly, it has been demonstrated that obese animals whose diet regimen is reversed from HFD back to standard chow, recover memory function [22].

3. Obesity, type 2 diabetes mellitus and leptin resistance

As mentioned above, obesity significantly increases cognitive decline and AD risk, supporting the notion that AD is a degenerative metabolic disease in which brain glucose uptake and utilization are impaired [30]. Thus, several early biomarkers rely on the definition of AD as a "Cognitive Metabolic Syndrome" or "Type 3 Diabetes" [31]. Biological plausibility for this relationship has been framed within the "Metabolic cognitive syndrome" concept. Even more, it has been proposed that Aβ accumulation can be considered a consequence rather than the real etiologic basis for the disease. A growing body of epidemiological evidence suggests that metabolic syndrome and its components (impaired glucose tolerance, abdominal or central obesity, hypertension, hypertriglyceridemia, and reduced high-density lipoprotein cholesterol) may be important in the development of age-related cognitive decline, mild cognitive impairment, vascular dementia, and AD [32]. Furthermore, results from the "Hysayama Study" indicate that altered expression of genes related to diabetes mellitus in AD brains is a result of AD pathology, which may thereby be exacerbated by peripheral insulin resistance or diabetes mellitus [33].

In fact, adults with newly diagnosed prediabetes, or type 2 diabetes mellitus (T2DM), show insulin resistance associated with reductions in regional cerebral glucose metabolism and subtle cognitive impairments [34]. Furthermore, most obese individuals show increased food intake despite high circulating Lep levels [35]. These findings imply a state of Lep resistance that causes a reduced responsiveness to Lep anorexigenic effect, with a concomitant loss of appetite- and weight gain-suppressing effects [36,37].

4. Leptin functions in the hypothalamus

The peripheral actions of metabolic hormones are well documented. However, the functions of these pleiotropic hormones are not restricted to the periphery, with growing evidence suggesting that both Lep and insulin can readily cross the BBB, producing widespread central effects in brain areas like the hypothalamus. In the periphery, the fat mass participates in the regulation of glucose and insulin metabolism through the release of hormones in a bidirectional feedback loop, a mechanism called the "Adipoinsular axis" (Fig. 1) [38,39]. This axis links adipose tissue and pancreatic β-cells via leptin and insulin, respectively. As insulin directly stimulates Lep release by adipose tissue, Lep feeds back to reduce both insulin secretion and insulin gene expression in β-cells by modulation of K^{+}_{ATP} channels and activation of cyclic nucleotide phosphodiesterase 3B and subsequent suppression of cAMP levels [40,41]. The suppressive effect of Lep on insulin production is not only mediated by direct actions via Lep receptors (LepR) on β-cells, but also by the autonomic nervous system (ANS). Lep-dependent ANS regulation of body weight is largely achieved via a negative afferent loop involving the hypothalamus [42,43].

It has been shown that hypercaloric diets (HCD) used in a majority of diet-induced obesity studies, typically induce glucose metabolism abnormalities and insulin resistance (including diabetes mellitus) and persistent hyperleptinaemia [44]. In addition, the consumption of Western diets, rich in sugar and saturated fat, stimulates an inflammatory response in the hypothalamus, a contributing factor to the development of central Lep resistance and obesity [36]. In the hypothalamus, specialized groups of neurons are sensitive to signals derived from several organs related to food intake or starvation. Hypothalamic pro-opiomelanocortin (POMC) and neuropeptide Y–Agouti-related peptide (NPY–AgRP) neurons produce anorexigenic and orexigenic neuropeptides and neurotransmitters, and express the long signalling form of the leptin receptor (LRb). The anorexigenic properties and the regulatory functions of Lep in the control of energy and glucose homeostasis are largely dependent on the POMC and NPY–AgRP circuits in the arcuate nucleus of the hypothalamus. POMC and NPY neurons are considered as major Lep effector sites, with the food-intake regulation directly dependent on the LRb/STAT3 (activator of transcription 3) interaction [45,46].

Recent evidence suggests that sirtuin-1 (SIRT1) activation and expression are essential for leptin-induced anorexigenic effects in the hypothalamic POMC neurons [47]. Moreover, results in Lep deficient ob/ob mouse model show a lack of SIRT1 activation in the hypothalamus in response to caloric restriction, compared to age-matched controls [48].