ADIPOKINE PATHWAYS ARE ALTERED IN HIPPOCAMPUS OF AN EXPERIMENTAL MOUSE MODEL OF ALZHEIMER’S DISEASE

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Abstract: A growing body of evidence suggests that β-amyloid peptides (Aβ) are unlikely to be the only factor involved in Alzheimer’s disease (AD) aetiology. In fact, a strong correlation has been established between AD patients and patients with type 2 diabetes and/or cholesterol metabolism alterations. In addition, a link between adipose tissue metabolism, leptin signalling in particular, and AD has also been demonstrated. In the present study we analyzed the expression of molecules related to metabolism, with the main focus on leptin and prolactin signalling pathways in an APPswe/PS1dE9 (APP/PS1) transgenic mice model, at 3 and 6 months of age, compared to wild-type controls. We have chosen to study 3 months-old APP/PS1 animals at an age when neither the cognitive deficits nor significant Aβ plaques in the brain are present, and to compare them to the 6 months-old mice, which exhibit elevated levels of Aβ in the hippocampus and memory loss. A significant reduction in both mRNA and protein levels of the prolactin receptor (PRL-R) was detected in the hippocampi of 3 months old APP/PS1 mice, with a decrease in the levels of the leptin receptor (OB-R) first becoming evident at 6 months of age. We proceeded to study the expression of the intracellular signalling molecules downstream of these receptors, including stat (1-5), sos1, kras and socs (1-3). Our data suggest a downregulation in some of these molecules such as stat-5b and socs (1-3), in 3 months-old APP/PS1 brains. Likewise, at the same age, we detected a significant reduction in mRNA levels of lrp1 and cyp46a1, both of which are involved in cholesterol homeostasis. Taken together, these results demonstrate a significative impairment in adipokine receptors signalling and cholesterol regulation pathways in the hippocampus of APP/PS1 mice at an early age, prior to the Aβ plaque formation.

Key words: APP/PS1, leptin, hippocampus, prolactin, Alzheimer.

Introduction

Alzheimer’s disease (AD) is the most common cause of senile dementia in the world, followed by Parkinson’s disease (1). AD progression is associated with the formation of senile β-amyloid (Aβ) plaques and neurofibrillary tangles composed of hyperphosphorylated tau (1, 2). Currently it is widely accepted that Aβ is generated by a specific proteolytic cleavage of the amyloid precursor protein (APP). In this amyloidogenic pathway, the β- and γ-Secretases cleave APP at the N- and C-termini of the Aβ peptide, respectively. The relationship between APP and Aβ caused the formulation of the amyloid cascade hypothesis that states that mutations in APP (or other genes) lead to an increase in Aβ, and that this in turn leads to disease progression (3, 4).

A number of animal models attempting to mimic the progression of the AD have been extensively investigated. APP/PS1 mice, which possess 2 of the more frequent mutations leading to familial AD (FAD) in humans, are commonly used in experimental animal studies of AD. One of the principal features of these mice is the development of memory loss and a significant Aβ plaque deposition in the hippocampus, clearly evident by 6 months of age (5-8). We have chosen to study 3 months-old animals which do not present brain Aβ deposits nor cognitive loss and we have compared them to the 6 months-old mice. The rationale behind this approach is to identify molecular events involved in the early pre-plaque stages of the AD-like pathology in this mouse model. In our opinion, this is especially relevant because despite the genetic and cell biological evidence that supports the amyloid hypothesis, it is becoming increasingly clear that AD aetiology is more complex and that Aβ alone is unable to account for all the aspects of AD (9). Hundreds of genes have been identified as being involved in this neurodegenerative disease (10, 11).

Recent studies suggest that metabolic alterations such as diabetes mellitus, cholesterol metabolism dysregulations and metabolic syndrome in general are strongly correlated with AD (11-17). Thus, a continuous effort should be made to identify components of the network involved in the progression of diseases like AD in order to develop more efficient and specific treatments (18-20).

Since the sporadic form of AD is a multifactorial disease influenced by several risk factors such as hypertension, diabetes, hypercholesterolemia, age, neuroinflammation, hypoxia and others, it is difficult to point out a single pathogenetic mechanism leading to the onset and progression
of this devastating disorder (6-8, 14-20). For example, obesity significantly increases cognitive decline and AD risk, supporting the notion that molecular mechanisms of cellular energy homeostasis are linked to AD pathogenesis (15-20). Additionally, there is evidence of a relationship between adipokines and AD (21-24). The adipokines or adipocytokines are cytokines secreted by adipose tissue (21). These include leptin, adiponectin, tumor necrosis factor (TNF)-alpha, interleukins, including IL-6, and also molecules like prolactin (Prl), a well-known regulator of the lactating mammary gland, recently shown to be produced by human adipose tissue (21-27). Adipokines have come to be recognized for their contribution to the mechanisms by which obesity and related metabolic disorders influence diseases like cancer or AD (24-28). It has been observed that AD patients display increased circulating levels of anorexigenic adipokines that may contribute to the metabolic changes observed in AD patients (21).

Among the adipokine genes associated to AD, an adipostatic hormone leptin, coded by the ob or lep gene, stands out. Leptin is a hormone secreted by adipose tissue that acts to suppress appetite and regulates energy expenditure. In humans, a correlation between elevated leptin levels and reduced incidence of dementia and AD had been reported (28). In rodents, leptin modulates production and clearance of Aβ (29-31). Mice with leptin receptor disruption show impairments in long-term potentiation, synaptic plasticity and spatial learning, whereas treatment with leptin increases Aβ- and tau- clearance as well as ameliorates AD-like pathology (21, 25-31). Thus, in the context of the amyloid cascade hypothesis, leptin may interfere with the pathogenesis of AD in multiple ways: (a) by inhibiting the amyloidogenic process; (b) by decreasing the activity of glycogen synthase kinase-3β (GSK3β), causing a reduction in Tau protein phosphorylation; and (c) by improving cognitive function (25-27).

Beside the roles of adipokines per se, it has been shown that alterations in lipid metabolism can also promote the development of AD. The brain is rich in cholesterol and substantial evidence from in vitro and in vivo studies, as well as from human trials, indicates that cholesterol levels affect the synthesis, clearance, and the toxicity of Aβ (13, 14, 32). For example, elevated cerebral Aβ levels in living humans were found to be correlated with serum cholesterol fractions in a pattern analogous to that found in coronary artery disease (11).

In the current study we have focused on molecular mechanisms related to adipokine signalling, AD progression and memory loss in the hippocampus of an APP/PS1 mouse model of FAD at two time points: 1) at 3 months of age, prior to the plaque formation and memory loss, and 2) at 6 months of age, by which both cognitive decline and hippocampal Aβ deposits are clearly evident.