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Adipokines in neurovascular diseases

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ABSTRACT

Adipose tissue is now described as an endocrine organ secreting a number of adipokines contributing to the development of inflammation and metabolic imbalance, but also endothelial dysfunction, vascular remodeling, atherosclerosis, and ischemic stroke. Leptin, adiponectin, and resistin are the most studied adipokines which play important roles in the regulation of cardiovascular homeostasis. Leptin and adiponectin mediate both proatherogenic and antiatherogenic responses. Leptin and adiponectin have been linked to the development of coronary heart disease and may be involved in the underlying biological mechanism of ischemic stroke. Resistin, a pro-inflammatory cytokine, is predictive of atherosclerosis and poor clinical outcomes in patients with coronary artery disease and ischemic stroke. The changes in serum levels of novel adipokines apelin, visfatin are also associated with acute ischemic stroke. These adipokines have been proposed as potential prognostic biomarkers of cardiovascular mortality/morbidity and therapeutic targets in patients with cardiometabolic diseases.

In this article, we summarize the biologic role of the adipokines and discuss the link between dysfunctional adipose tissue and metabolic/inflammation imbalance, consequently endothelial damage, progression of atherosclerotic disease, and the occurrence of ischemic stroke.

1. Introduction

Adipose tissue is an active secretory organ that releases a variety of messenger molecules. Adipocyte-derived hormones have structural homology to cytokines that actively participate in the regulation of many biological processes. Major target receptors for the messenger molecules are located in adipose tissue and they are also found in the hypothalamus, skeletal muscle, and liver. Adipokines can also exert

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endocrine effects and participate in an interplay between several tissues [1,2].

The diversity of adipokines, both in terms of protein structure and of putative function, is considerable. The group includes: classical cytokines (e.g., tumor necrosis factor TNFα, IL-6), specific chemokines (IL-8, monocyte chemoattractant protein MCP-1, macrophage inflammatory protein MIP-1a, MIP-2a, stromal cell-derived factor SDF-1), growth factors (e.g., transforming growth factor-b; TGF-b) and proteins of the alternative complement system (e.g., adipsin, acylation-stimulating protein). The group also includes: proteins involved in vascular hemostasis (e.g. plasminogen inhibitor-activator -1 PAI-1, tissue factor), lipid metabolism (leptin, retinol-binding protein, cholesteryl ester transfer protein), glucose homeostasis (e.g., adiponectin, possibly resistin) and angiogenesis (e.g., vascular endothelial growth factor; VEGF), as well as acute-phase and stress responses (e.g., haptoglobin, metallothionein) [3,4].

Whether adipokines are obesity-dependent or independent risk factors for neurology diseases, and how adipokines coordinately regulate physiological functions is not yet clear. However, link between obesity-associated systemic inflammation and cerebrovascular, autoimmune and degenerative neurology disorders has become of major interest [2,5,6]. Fig. 1 describes the role of obese adipocytes in the inflammation and pathogenesis of atherosclerosis.

2. Role of adipose tissue in cerebrovascular disorders

Stroke, a leading course of death and disability, shares many risk factors with cardiovascular diseases (CVD), such as are age, smoking, hypertension, inactivity, overweight or obesity, and dyslipidemia. The role for adipose tissue in ischemic stroke remains largely unknown [7]. It is accepted that individuals with metabolic syndrome (MetS) are at an increased risk for developing type 2 diabetes mellitus. Type 2 diabetes mellitus is a secondary risk factor for atherosclerosis and is linked with a 2–3 fold elevated risk of developing CVD morbidity and mortality [8]. Moreover, results published by Kontoangelos et al. [9] show that IL-6, IL-12 and TNF-α are closely related to the pathogenesis of type 2 diabetes. In regard to MetS, obesity and notably abdominal obesity is associated with increases CVD risk through its effects on elevated blood pressure, impaired glucose tolerance, insulin resistance, and consequent changes including dyslipidemia (elevated triglycerides and LDL-cholesterol plasma concentrations), endothelial dysfunction, or oxidative stress [8]. These are summarized in Fig. 2.

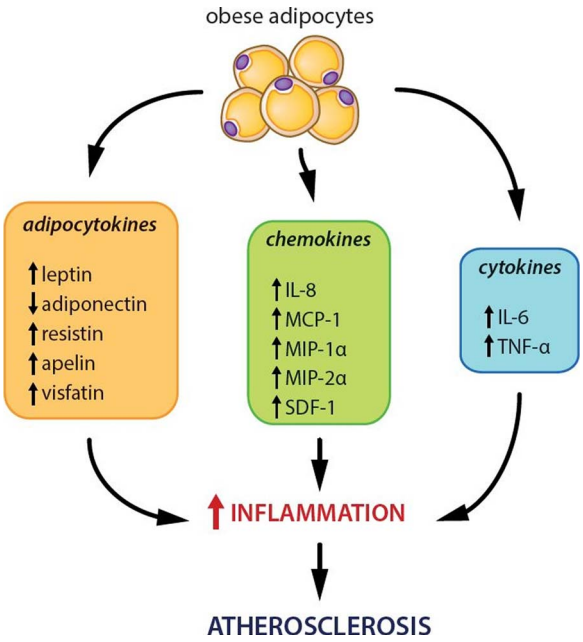

Fig. 1. The basic role of adipocyte dysfunction in the pathogenesis of atherosclerosis. IL, interleukin; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; SDF, stromal cell-derived factor; TNF, tumor necrosis factor.

Some studies suggest that obesity is an independent risk factor for cerebrovascular disease [7,10–13]. The measures of obesity include body mass index (BMI), waist-to-hip ratio, waist circumference (WC). BMI help to classify rate of excess of adipose-tissue mass as overweight when body mass index (BMI) is > 25 kg/m^2, and as obesity when BMI > 30 kg/m^2 [7,10]. Study results are not always conclusive, showing controversial data. For example, markers of abdominal adiposity have shown a graded and significant association with risk of stroke, independent of other vascular risk factors. Among them predictive function of WC for cerebrovascular events has been found even better than BMI [13]. On the other hand, one of the studies has proved higher BMI, especially BMI > 30 kg/m^2 in male subjects to be associated with an increased risk of cerebrovascular accidents [14]. Controversially, Wannamethee and colleagues have reported BMI and WC not to be associated with risk of stroke in older men, although obese men (BMI > 30 kg/m^2) showed the lowest risk of stroke [15], yet women were excluded from this study. The findings were consistent with previously reported studies that have shown no association of obesity and stroke in older men [16,17]. The phenomenon called "obesity paradox" that has been described moreover in older patients, may reflect changes of body morphology in the elderly [15].

Association of excessive body weight and carotid artery disease indicates positive role of obesity in development of stroke [18]. The diameter and stiffness of carotid arteries have appeared increase with higher BMI. Carotid distensibility decreased more with BMI at young than old age. In elastic arteries, the relationship between arterial stiffness and BMI was more complex with gender and age [18].

An excess of white adipose tissue (WAT) releases adipokines, including leptin, adiponectin, resistin and visfatin, that have been associated with cerebrovascular diseases [19]. Here, we will discuss the adipokines that are associated with ischemic stroke or other cerebrovascular disorders.

3. Cerebrovascular diseases and adipokines

3.1. Leptin

Leptin (LEP) is expressed mostly in adipose tissue, although low levels have been found in other organs [20]. It circulates bound and in the bioavailable unbound form. LEP concentration is dependent on the quantity of stored fat, as well as the status of energy balance. As such, plasma leptin is higher in obese than in lean individuals, falls rapidly during fasting, and increases after feeding. Leptin acts primarily in the brain, binding to receptors in the lateral hypothalamus [1,20]. A study evaluating leptin level differences between serum and cerebrospinal fluid (CSF) found that CSF levels have a tendency toward higher levels in women than men. CSF leptin was, in contrast to plasma levels, positively correlated with BMI in both men and women [21].

LEP is implicated in direct regulation of adipose tissue metabolism by both inhibiting lipogenesis and stimulating lipolysis [19]. Experiments demonstrate cross-talk between lipids and leptin circulation. Triglycerides are capable to reduce leptin transport across the blood brain barrier and modulate function of hypothalamic centers. The presence of higher plasma triglyceride levels in obese individuals is therefore thought to be directly responsible for the lack of brain leptin concentration and leptin resistance [22].

LEP acts also under the influence of endocrine system. LEP levels are increased by glucocorticoids, insulin release, TNFα, IL-1 and by ovarian sex steroids. LEP levels decrease under the effect of catecholamines, triiodothyronine (T3) and thyroxine (T4), cyclic adenosine monophosphate (cAMP) and androgens [23]. Thus LEP may be a key factor for the development of the multiple neuroendocrine abnormalities that are observed after stroke, including cortisol axis regulation. Increased