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Review Article

Salusins and adropin: New peptides potentially involved in lipid metabolism and atherosclerosis

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ABSTRACT

Dyslipidemia is one of the most potent risk factors for the development of atherosclerosis. The high atherosclerotic risk in dyslipidemic patients is associated with endothelial dysfunction. During the last two decades, novel bioactive peptides have emerged as potential biomarkers of endothelial dysfunction and dyslipidemia-salusins and adropin. Salusin-alpha is likely to prevent atherosclerosis, while salusin-beta may act as a potential proatherogenic factor. Adropin was recently identified as important for energy homeostasis and lipid metabolism. Adropin is closely related to the inhibition of atherosclerosis by up-regulation of the endothelial nitric oxide synthase expression through the vascular endothelial growth factor receptor-2. These peptides represent a novel target to limit diseases characterized by endothelial dysfunction and may form the basis for the development of new therapeutic agents for treating metabolic disorders associated with atherosclerosis.

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Contents

1. Introduction

The prevalence of atherosclerosis and its complications have increased substantially in recent decades [1]. Atherosclerosis is associated with cardiovascular diseases [1] and is an indirect cause of a high death rate in the general population [2]. Dyslipidemia is one of the most important factors incriminated in the development of atherosclerosis [3,4]. There are several conditions already established as associated with dyslipidemia, endothelial dysfunction and consequently atherosclerosis (diabetes, high blood pressure, cigarette smoking, obesity, hyperuricemia [5,6]). However, in the last decade novel peptides have emerged as potential biomarkers of lipid and atherosclerotic disturbances: irisin,

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endothelin, visfatin, vaspin as well as recently described salusins and adropin [7–12]. Pathogenesis of atherosclerosis is a multifactorial process involving several biochemical and signaling pathways. The progression of this disease is modulated by products of inflammatory cells, such as vasoactive mediators, cytokines and several proteins [13,14]. Some of these molecules can be regarded as potential therapeutic targets to improve treatment of atherosclerosis.

In this review, we have shown the results of recent investigations concerning physiological and biochemical properties of salusins and adropin as novel regulators of dyslipidemia, atherosclerosis, and other metabolic disorders.

2. Review

2.1. Salusins

There are two forms of salusin: salusin-alpha and salusin-beta. Salusin-alpha is likely to prevent atherosclerosis [11], while salusin-beta may act as a potential proatherogenic factor [15]. Salusins belong to a new class of peptides discovered by bioinformatics analysis of a full-length cDNA library. Shichiri et al. [16] identified and characterized two related peptides of 28 and 20 amino acids designated salusin-alpha and salusin-beta, respectively. These peptides are considered to be biosynthesized from preprosalusin, an alternative-splicing product of the torsion dystonia-related gene (TOR2A), after frameshift reading and digestion at dibasic amino acids [16]. Salusin-beta contains more hydrophobic amino acids residues than salusin-alpha. Both salusins have distinct physicochemical properties [16]. Although each salusin likely binds to its respective cell surface binding sites, their specific receptors have not been identified [17]. These bioactive peptides are synthesized in many tissues, including these of the small intestine, stomach, adrenal medulla, thymus, lymph nodes, spleen, bone marrow, salivary glands, lungs, skeletal muscle, testes, heart, adrenal cortex, liver, brain, human vascular smooth muscle cells (VSMCs), and endothelial cells [17–19]. In the liver, Kupffer and hepatocellular cells synthesize both salusin-alpha and salusin-beta [18]. Interestingly, salusins are also expressed in human atherosclerotic plaques [11]. Salusins were found in biological fluids such as blood and urine [16,19,20].

2.1.1. Salusins, lipids and atherosclerosis

There are only few studies investigating an association between lipid components, atherosclerosis, and salusins. In 2008, Watanabe et al. [11] demonstrated on human macrophage foam cells, that salusin-alpha and salusin-beta induce opposite effects on foam cell formation – a process that is crucial for the development of atherosclerotic plaques [21]. Salusin-alpha suppressed human foam cell formation by down-regulation of acyl-coenzyme A: cholesterol acyltransferase-1 (ACAT-1), an enzyme stimulating the accumulation of cholesterol esters in macrophages. In contrast, salusin-beta increased the formation of human foam cells by up-regulating ACAT-1 [11]. The regulation of ACAT-1 expression by salusins was mediated through the G-protein/c-Src/PKC/MAPK signaling pathway [11]. Therefore, results of Watanabe et al. [11] strongly suggested that salusin-alpha was likely to prevent atherosclerosis, while salusin-beta could be a potential proatherogenic factor. Moreover, this suggestion was supported by the same authors in studies on patients suffering from coronary artery disease (CAD). Serum salusin-alpha levels were significantly lower in patients with angiographically proven CAD than in non-CAD subjects [11], whereas serum levels of salusin-beta were significantly higher in patients with angiographically proven CAD compared to subjects without CAD [22]. Additionally, decreased levels of serum salusin-alpha were associated with carotid atherosclerosis and cardiac dysfunction in patients with essential hypertension, and a significant positive correlation between serum salusin-alpha and high density lipoprotein (HDL) cholesterol levels was shown in these hypertensive patients [23].

Many studies have shown that polycystic ovary syndrome (PCOS) is associated with various cardiovascular risk factors such as obesity, insulin resistance, hyperlipidemia, metabolic syndrome, endothelial dysfunction, and hypertension. Pathogenetic mechanisms of these disturbances are not completely clarified yet, but insulin resistance appears to play a critical role [24,25]. In patients with PCOS, serum salusin-beta is higher in comparison to healthy woman and correlated positively with triglycerides (TG) and low density lipoprotein (LDL) cholesterol [26].

Kołakowska et al. [27] studied 88 children and adolescents with essential hypertension. They found that serum salusin-beta positively correlated with TG level and TG/HDL cholesterol ratio.

In our study [28] on dyslipidemic patients treated with hemodialysis (HD) due to end-stage renal disease, we showed a negative correlation between salusin-alpha and LDL cholesterol and positive with HDL cholesterol/LDL cholesterol ratio. Lifestyle interventions (lipid-lowering diet and increased physical activity) or administration of atorvastatin resulted in changes of serum salusin-alpha levels and lipid profiles in this group. A lifestyle-induced improvement in the serum lipid profile was associated with a decrease in plasma salusin-alpha level, possibly due to amelioration of salusin-alpha up-regulation by dyslipidemic conditions. An increase in salusin-alpha during treatment with atorvastatin was explained by a specific atorvastatin effect on the secretion of salusin-alpha.

The inverse effects of salusin-alpha and salusin-beta on formation of atherosclerotic lesions were confirmed in animal studies [29]. In apolipoprotein E-deficient (ApoE−/−) mice, significantly enhanced atherosclerotic lesions in the aorta and macrophage infiltration into the lesions without affecting blood pressure or serum total cholesterol and glucose levels were detected after 4- and 8-week infusion of salusin-beta [29]. On the contrary, infusion of salusin-alpha for 4- and 8-weeks significantly suppressed aortic atherosclerotic lesions by decreasing macrophage foam cell formation associated with ACAT1 down regulation (oxidized LDL-induced cholesterol ester accumulation in macrophages was decreased). Cluster of differentiation 36 (CD36) expression by exudate peritoneal macrophages was not influenced under these conditions, but serum lipid profile showed beneficial changes (significantly increased serum HDL cholesterol levels and decreased non-HDL cholesterol levels) [29]. In other study, the expression of salusin-beta was increased in atherosclerotic lesions in LDL receptor-deficient [LDLR(−/−)] mice. Subcutaneous injections of salusin-beta, once a day for 12 weeks, into LDLR(−/−) mice, aggravated atherosclerotic lesions, and this effect was associated with significantly increased serum LDL cholesterol level [15]. Other investigators [30] examined whether salusin-beta plays a role in myocardial remodeling after myocardial ischemia reperfusion injury in the rat model. They administered the neutralizing salusin-beta antibody, once daily from day 1 to day 7 after ischemia reperfusion. The anti-salusin-beta therapy enhanced myocardial angiogenesis in the peri-ischemic area of reperfusion. The authors clarified that endogenous salusin-beta suppresses angiogenesis which is critical in the development of cardiac remodeling injury.

Proliferation of VSMCs is closely linked with atherosclerosis [31]. Salusin-beta stimulates proliferation of VSMCs and vascular fibrosis in rats and humans [32]. In contrast, salusin-alpha has marginal mitogenic effects in these cells [16].

Analyzing the current studies on salusins and their relationship with atherosclerosis and lipid disturbances, it can be assumed that the metabolic dependency may exist between them. Increased

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