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Review Article

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

Leszek Niepolski [a,*], Alicja E. Grzegorzewska [b]

[a] B. Braun Avitum Poland, Dialysis Center, Nowy Tomyśl, Poland
[b] Department of Nephrology, Transplantology and Internal Diseases, Poznan University of Medical Sciences, Poznań, Poland

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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.

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,

* Corresponding author at: B. Braun Avitum Poland, Dialysis Center, Sienkiewicza str. 3, 64-300 Nowy Tomyśl, Poland. Tel.: +48 61 44 27 180; fax: +48 61 44 27 181.
E-mail address: leszek.niepolski@avitum.com.pl (L. Niepolski).

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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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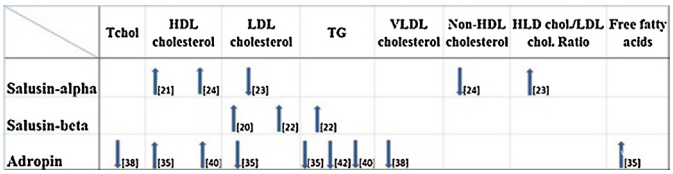

Fig. 1. The summary of the relationships between described peptides and lipid components. HDL – high density lipoprotein; LDL – low density lipoprotein; Tchol – total cholesterol; TG – triglycerides; VLDL – very low density lipoprotein.

expression of salusin-alpha is rather associated with better lipid profiles, whereas increased expression of salusin-beta is associated with worse lipid profiles (Fig. 1). The exact relationship and mechanisms by which salusins affect lipid metabolism and atherosclerosis remain unclear. Future studies are needed to solve these issues.

In summary, current evidence indicates that salusin-beta and salusin-alpha may contribute to proatherogenesis and antiatherogenesis, respectively, in human subjects (Fig. 2).

2.1.2. Salusins and blood pressure

Initial studies indicated salusins as multifunctional regulators of hemodynamics [16]. Salusin-beta appeared as a potent hypotensive factor. This peptide rapidly induced hypotension, bradycardia, and cardiac function by a cholinergic mechanism [33]. Circulating levels of salusin-alpha were shown to be significantly associated with the left ventricular dysfunction [34]. The hypertensive patients with left ventricular hypertrophy (LVH) showed lower serum salusin-alpha level in comparison to non-LVH group. In both groups, serum salusin-alpha was negatively correlated with left ventricle mass index and brachial-ankle pulse wave velocity [34]. The expression of salusin-alpha may be inhibited by the activation of Janus kinase 2 (Jak-2), which is expected to be up-regulated by angiotensin II, inflammatory cytokines, and growth factors in atherosclerotic and hypertensive diseases [36].

2.1.3. Salusins and metabolic syndrome

Hypertension and dyslipidemia often coexist with hyperglycemia and abdominal obesity in metabolic syndrome (MeS) [36,37]. In the Sprague-Dawley rat model with MeS induced by fructose, the expression of salusins was reduced in the liver (the site of many biochemical processes) and brain (which controls much of the endocrine system) tissues [18]. Further elucidation of mechanisms of salusin action is needed for better understanding of the role of these peptides in the development of MeS.

2.2. Adropin

Adropin was identified during investigation of obese insulin resistant mice as a novel factor linking signals of nutrient intake with metabolic homeostasis [12]. It is a small peptide encoded by energy homeostasis associated gene (*ENHO*) that is expressed mainly in the liver and brain. *ENHO* is located in chromosome 9p13.3, and is involved in the regulation of glucose homeostasis and lipid metabolism. Adropin is a 76 amino acid polypeptide with the first 33 residues comprising the signal peptide, and has a molecular weight of 4999 Da [12]. Human, mouse, and rat adropin amino acid sequencing are 100% identical. The half-life of adropin has not been identified yet. However, it is assumed that the half-life of this peptide is as short as several minutes [38]. Adropin is important for energy homeostasis [12], lipid metabolism [12], and maintaining insulin sensitivity [39].

The role of adropin in metabolism is supported by the observation that therapy with synthetic peptide improves glucose homeostasis, fatty liver, and dyslipidemia observed in mouse models of obesity [12]. Additionally, lower adropin levels were associated with insulin resistance in humans as well as in mice [12,40]. Elevated amounts of adropin in circulation reduce insulin resistance that occur in response to metabolic stress [12,39,40].

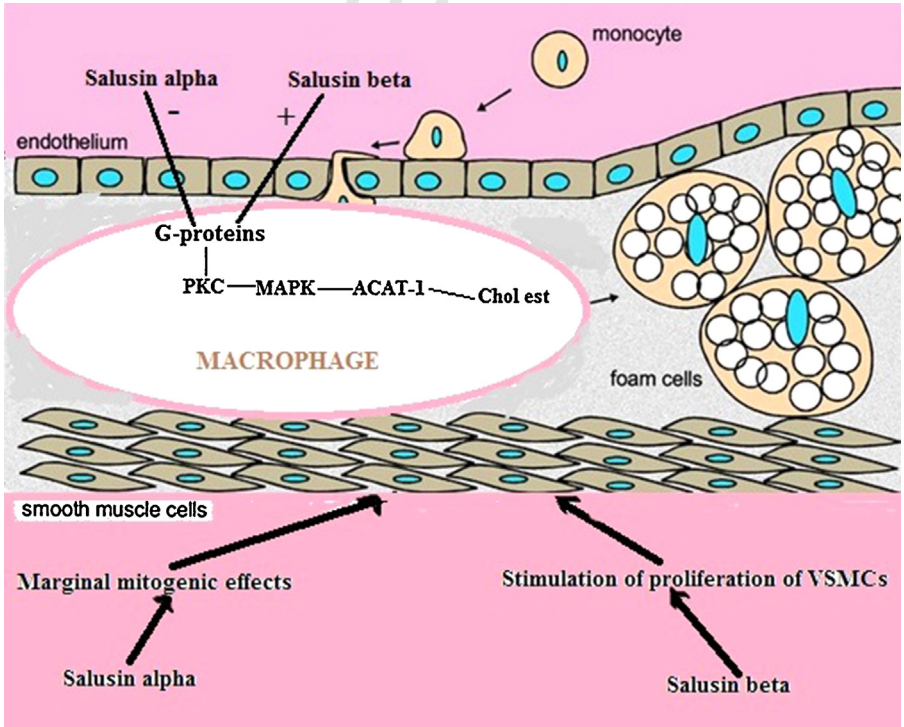

Fig. 2. Salusin alpha and salusin beta signaling pathways involved in the development of atherosclerosis. ACAT-1 – acyl-coenzyme A: cholesterol acyltransferase-1; Chol.est – cholesterol esters; MAPK – mitogen-activated protein kinases; PKC – protein kinase C; VSMCs – vascular smooth muscle cells.

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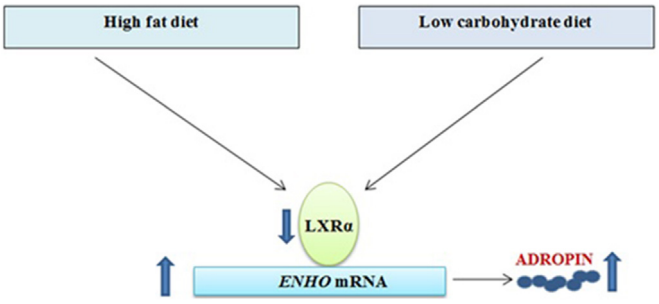

Fig. 3. A scheme of showing an influence of dietary components on the expression of *ENHO* and secretion of adropin in the liver. *ENHO* – energy homeostasis associated gene; LXRα – liver X receptor alpha.

2.2.1. Adropin, nutritional state and obesity

In adropin knockout (AdrKO) mice, Kumar et al. [39] showed that serum adropin levels were elevated proportionally to the increase in dietary fat content. High adropin levels were found in mice fed a high fat and low carbohydrate diet, while lower levels were observed in mice fed a low fat and high carbohydrate diet (Fig. 3). Additionally, adropin protected against obesity-associated hyperinsulinemia and hepatosteatosis by regulating the lipid and glucose metabolism [39]. Lifelong calorie restriction led to metabolic adaptation and re-programming of the hepatic fat metabolism in mice through the reduction of lipogenesis and stimulation of lipolysis and ketogenesis [12]. In this study, adropin significantly correlated with the diminution of lipogenesis. This diminution was substantiated by decreased expression of liver X receptor alpha (LXRα). Based on these observations, it can be assumed that obesity is associated with lower circulating adropin concentrations in mice. To check an impact of weight changes on adropin production in humans, other researchers [40] examined how weight loss after Roux-en-Y gastric bypass affected adropin levels. Adropin concentrations increased after the bypass surgery and reached a peak in the post-operative 3rd month.

2.2.2. Adropin, insulin resistance and diabetes mellitus

Recent findings concerning insulin resistance and diabetes mellitus suggest that peptides (*e.g.* irisin, vaspin, visfatin) secreted by several tissues (muscles, liver, fatty tissue) regulate lipid and carbohydrate metabolism in key insulin-targeted tissues [7,9,10]. However, a relationship between adropin, insulin resistance and glucose tolerance is not clearly defined [41–43]. Changes in adropin expression were examined in the brain, cerebellum, kidney, heart, liver, and pancreas of rats after streptozotocin-induced diabetes. Tissues of diabetic rats synthesized more adropin, and their serum adropin was increased compared to controls [44]. The clinical study on patients with normal renal function, revealed that serum adropin level was significantly lower in type 2 diabetes mellitus (T2DM) patients than in those without diabetes [43]. The preliminary study on uremic patients treated with HD showed no significant difference in plasma adropin levels between subjects with T2DM and without diabetes [45]. In HD patients without diabetes, plasma adropin level correlated negatively with plasma insulin level and with insulin resistance evaluated by the homeostatic model assessment of insulin resistance (HOMA-IR), but this phenomenon was not shown in T2DM subjects. The study conducted in women with gestational diabetes mellitus (GDM) and healthy pregnant women showed that mothers with GDM had lower adropin concentrations in their blood [41]. Similarly, serum adropin levels were lower in women with PCOS than in the control group. The lower plasma adropin concentrations in patients with GDM and PCOS in comparison to healthy population may be explained by carbohydrate intolerance present in both these diseases. Additionally, in woman with PCOS, serum adropin level correlated negatively with fasting serum insulin levels and HOMA-IR [42].

2.2.3. Adropin and endothelial function

Insulin resistance and vascular function are closely related. Therefore, one can suspect that adropin may also exert a direct effect on the endothelial cell metabolism. In the cell culture model, adropin-treated endothelial cells demonstrated greater proliferation and migration. Adropin could exert its impact on cell functions by the up-regulation of endothelial nitric oxide synthase (eNOS) expression through the vascular endothelial growth factor receptor 2 (VEGFR2) *via* phosphoinositide 3-kinase (PI3K/Akt) and extracellular signal-regulated kinases 1 and 2 (ERK1/2) signaling pathways in endothelial cells (Fig. 4). Thus, adropin may be a novel regulator of eNOS *via* these dual pathways. These findings collectively suggest that adropin may be a trigger of the VEGFR2 – PI3K/Akt and – ERK1/2 signaling pathways in endothelial cells. These observations are consistent with the fact that gene silencing VEGFR2 (using transfection medium) significantly impaired the effects of adropin [46].

2.2.4. Adropin, atherosclerosis and cardiovascular disease

Adropin, by up-regulation of eNOS, is involved in the endothelial function and the inhibition of atherosclerosis [46]. The transcript (mRNA) analyses revealed that adropin is expressed in human coronary artery endothelial cells [46]. Therefore, this peptide may be an important, unfavorable component of cardiometabolic diseases [46]. This thesis was supported by the clinical study of Yu et al. [47]. They found that patients with stabile ischemic heart disease have lower serum adropin concentrations compared to the matched control group, and patients with myocardial infarction have lower adropin concentrations than patients with stabile ischemic heart disease. Saphenus vein grafts (SVG) are frequently used in coronary artery bypass grafting (CABG). Late SVG occlusion is an important predictor of morbidity after CABG [48]. Demircelik et al. [49] showed that serum adropin

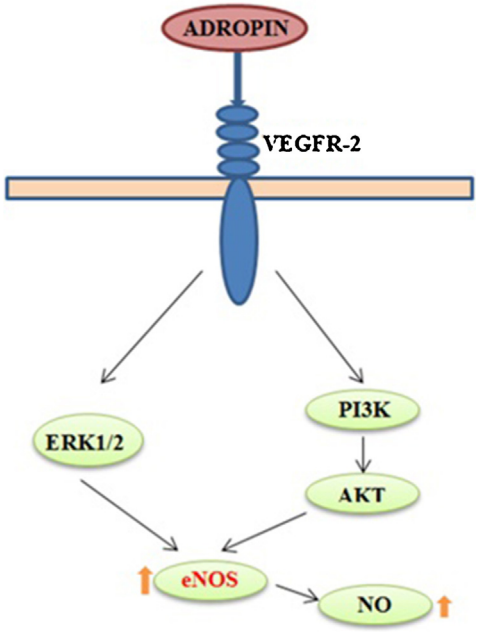

Fig. 4. A flowchart of showing adropin signaling pathway in endothelium. In endothelial cells, adropin up-regulates endothelial nitric oxide synthase (eNOS) expression through the vascular endothelial growth factor receptor 2 (VEGFR2) *via* phosphoinositide 3-kinase (PI3K/Akt) and extracellular signal-regulated kinases 1 and 2(ERK1/2) signaling pathways.

levels are lower in patients with late SVG occlusion in comparison with the group with patent SVG. They concluded that circulating adropin level may be a novel marker of SVG occlusion.

CAD is often associated with insulin resistance and T2DM. However, it is not known whether the coexistence of CAD and T2DM potentiates a diminution of adropin levels. Recently, Wu et al. [43] showed that serum adropin levels were significantly lower in T2DM than in non-diabetic individuals, and were associated with coronary atherosclerosis in T2DM and non-diabetic patients. Other researchers also showed that lower serum adropin levels were significantly associated with CAD [50] and positively correlated with flow-mediated dilatation values [51]. These authors asserted that lower adropin levels might be a novel predictor of coronary atherosclerosis and a novel biomarker in quantifying endothelial function. It is well established that endothelial dysfunction is one of the main underlying reasons not only for angina pectoris [52] but also for cardiac syndrome X (CSX) [53]. It was shown that serum adropin levels were significantly lower in patients with CSX than in healthy subjects. Therefore, adropin was established as an independent risk factor for CSX [53].

2.2.5. Adropin and lipid metabolism

ENHO is associated with carbohydrate and lipid metabolism. As previously mentioned, *ENHO* mRNA is regulated by LXRα, a nuclear receptor involved in expression of enzymes important for cholesterol and triglyceride metabolism [12]. LXRα agonists rapidly reduced the expression of *ENHO* mRNA in cultured cells and in the liver of mice. Therefore, stimulation of LXRα suppresses hepatic *ENHO* expression, and consequently adropin synthesis.

Glucose consumption lowers while fructose increases plasma adropin concentrations in humans [54]. Glucose passes through the liver and is readily oxidized as needed or converted to glycogen. In contrast, fructose is retained by the liver and is more readily converted to fatty acids and exported as very low density lipoproteins (VLDL). Consumption of diets with high fructose content has been suggested to promote the risk of metabolic diseases and adropin can act as a link between fructose and systemic TG metabolism [55].

Hepatic expression of *ENHO* and secretion of adropin by the liver is proposed to be involved in peripheral lipid homeostasis [12]. However, the association between adropin expression and serum lipid components remain unclear. There are only a few studies that evaluated this relationship. In patients who had acute myocardial infarction, serum adropin levels were negatively associated with triglyceride levels [47]. These results are in accordance with the previous study by Butler et al. [40], who demonstrated that adropin levels correlated negatively with triglycerides, LDL cholesterol, and ApoB levels in MeS patients after gastric bypass surgery. Additionally, positive associations of adropin with HDL cholesterol and free fatty acids were revealed in this study. Butler et al. [40] assumed that adropin may affect lipids metabolism (synthesis or clearance). In women with PCOS, serum adropin levels correlated negatively with total cholesterol, VLDL, and triglycerides [42]. The preliminary study on HD patients demonstrated that plasma adropin levels negatively correlated with TG and positively with HDL cholesterol in T2DM subjects [56].

Based on the mentioned studies it can be hypothesized that therapies addressing adropin could improve endothelial function, promote angiogenesis, retard atherosclerosis, and decrease the risk for the development of lipid abnormalities and insulin resistance.

3. Conclusions

In summary, the pathogenesis of atherosclerosis is multifactorial, but at every step of this process, dyslipidemia or the imbalance between proatherogenic and antiatherogenic factors accelerate atherosclerosis. Salusin-alpha and salusin-beta show contrasting effects on atherosclerosis. They possess antiatherogenic and proatherogenic properties, respectively. Adropin seems to have a protective effect in relation to endothelial cells. Therefore, salusin- and adropin-based treatments could emerge as a new line of therapy against atherosclerosis and related diseases.

Conflict of interests

The authors declare no conflict of interests.

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