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A novel peptide adropin in cardiovascular diseases

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ABSTRACT

Cardiovascular diseases, such as atherosclerosis and hypertension, are the major cause of mortality and morbidity in the world. Adropin was first discovered in 2008 by Kumar and his coworkers. Adropin, encoded by the Energy Homeostasis Associated gene, is expressed in many tissues and organs, such as pancreatic tissue, liver, brain, kidney, endocardium, myocardium, and epicardium. In this review, we have summarized recent data suggesting the roles of adropin in several major cardiovascular diseases. Increasing evidence suggests that adropin is a potential regulator of cardiovascular functions and plays a protective role in the pathogenesis and development of cardiovascular diseases. However, further studies are needed to elucidate the specific mechanisms underlying the association between adropin and cardiovascular diseases.

Contents

Abbreviations: DIO, diet-induced obesity; HFD, high-fat diet; CR, calorie restriction; LXR, liver X receptors; FXR, farnesoid X receptor; STZ, streptozotocin; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; PUFAs, polyunsaturated fatty acids; MetS, metabolic syndrome; ECs, endothelial cells; eNOS, endothelial nitric oxide synthase; VEGFR2, vascular endothelial growth factor receptor 2; ERK1/2, extracellular signal-regulated kinase 1/2; PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; SIRT1, silent information regulator 1; PGC-1α, peroxisome proliferators-activated receptor-γ coactivator-1α; Cpt1b, carnitine palmitoyltransferase 1B; Pdk4, pyruvate dehydrogenase kinase; PTEN, phosphatase and tensin homolog deleted on chromosome ten; PIP3, phosphatidylinositol-3,4,5-trisphosphate; PDH, pyruvate dehydrogenase; GLUT4, glucose transporter 4; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; IP3, inositol trisphosphate; LPL, lipoprotein lipase; VSMC, vascular smooth muscle cell; AdrKO, adropin knockout mice; GDM, gestational diabetes mellitus; iNOS, inducible nitric oxide synthase; NAFLD, nonalcoholic fatty liver disease; CAD, coronary artery disease; SCAD, stable coronary artery disease; AMI, acute myocardial infarction; SAP, stable angina pectoris; CSX, cardiac syndrome X; HF, heart failure; ET-1, endothelin-1; BNP, brain natriuretic peptide; BMI, body mass index; SBP, systolic blood pressure.

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1. Introduction

The incidence of cardiovascular diseases, the major cause of mortality and morbidity in the world, is influenced by the aging of the population, genetic predisposition, changing lifestyles, stress, hypercholesterolemia, dietary habits, diabetes and risky behaviors, including smoking, alcohol abuse, overnutrition and sedentary lifestyles. The increase in cardiovascular disease is already not some local or national phenomena, but a kind of universal existence, which severely impairs humanity health disease.

Adropin was first discovered in 2008 by Kumar and his coworkers in mice [1,2]. It was named after two Latin words: one is "aduro" (set fire to), and the second is "pinquis" (fats or oils). In addition to pancreatic, liver, brain and kidney tissues, the expression of adropin was demonstrated immunologically in the endocardium, myocardium, and epicardium [3]. There is growing evidence suggesting that adropin is a potential regulator of cardiovascular functions and plays a protective role in the pathogenesis and development of cardiovascular diseases [2]. In the present review, we summarized the molecular characterization, regulation, cellular signaling pathways and cardiovascular physiological actions of adropin, and also explored its emerging pathogenetic significance and therapeutic potential in cardiovascular diseases.

2. Structure and characterization

Adropin is encoded by the Energy Homeostasis Associated gene (gene symbol: Enho) that is expressed in the liver and brain [1]. The Enho gene maps to chromosome 9p13.3 and consists of 25 exons. Adropin contains 76 amino acids and has a molecular weight of 4.5 kDa [4]. Bioinformatics analysis using SignalP 3.0 and experiments both suggested that the adropin is likely (87% probability) to be secreted [1]. In the brain of mice, however, adropin is a membrane-bound protein. The N-terminus from amino acids 1–9 is localized in the cytoplasm. Evidence suggests that the region of amino acids 9–30 is the transmembrane domain, and is enriched in hydrophobic residues (including seven leucine, three isoleucine, and three valine residues of 21 amino acids) with a very poorly defined protease cleavage site [5–8]. The C-terminus from amino acids 30–76 is localized outside of the surface of the plasma membrane [9]. These controversial findings regarding circulating adropin will require further investigation into its biochemical properties. Adropin amino acid sequences in human, mouse, and rat are completely identical. Porcine adropin cloned by the pEnho shows high overall identity (98%–99%) with other known adropins [10].

Adropin exerts various effects on the body system. In metabolic homeostasis, for example, adropin improves glucose homeostasis, fatty liver, and dyslipidemia resulting from obesity. When Kumar and his coworkers firstly discovered adropin, they revealed that adropin regulation of glucose homeostasis was independent of changes in body weight, food intake, and whole body energy expenditure. They also found that adropin delayed DIO (diet-induced obesity) in mice primarily due to altered metabolism. The Enho gene-encoded adropin was also expressed in several areas of the brain involved in metabolic regulation [1]. The expression of adropin in the central nervous system suggests a role as a neuropeptide. It is also possible that adropin has autocrine/paracrine effects in peripheral tissues. Adropin not only regulates angiogenesis but also increases blood flow and capillary density in the model of hind limb ischemia [2]. In a recent study, it was observed that adropin was increased in plasma in patients with heart failure [11], suggesting the relevance of adropin to cardiovascular health.

3. Regulation of adropin expression

When adropin was discovered by Kumar and his colleague, it was shown that hepatic Enho expression is influenced by fasting, and the macronutrient composition of the diet with high expression levels observed during short-term ingestion of high-fat diet (HFD). However, chronic exposure to HFD is associated with reduced expression of adropin, suggesting deregulation of liver Enho expression in obesity [1]. It was reported that high adropin levels have been observed in mice fed a high-fat low carbohydrate diet, whereas lower levels of adropin have been observed in mice fed a low fat high carbohydrate diet [4]. The lifelong calorie restriction (CR)-induced increase in adropin levels may provide additional protection for the liver against an age-associated fat accumulation [12]. Taken together, this evidence suggests that adropin is associated with the fat in diets.

In addition, liver Enho mRNA expression can be rapidly upregulated by macronutrient contents, suggesting an involvement of intracellular lipid sensors [4]. The liver X receptors (LXRα and LXRβ) and farnesoid X receptor (FXR) are nuclear receptors that are regulated by sterols and bile acids, and involved in carbohydrate and lipid homeostasis [13]. In HepG2 cells, Enho expression was reduced by the LXR agonist (GW3965), which can be blocked by an antisense RNA targeting LXRα [14]. In mice treated with GW3965, liver Enho mRNA was also significantly reduced. There was no change in Enho expression observed, when HepG2 cells were treated with the FXR agonist (GW4064) [1]. Taken together, these results indicate that liver Enho mRNA expression is regulated by LXRα, but not FXR, a nuclear receptor involved in cholesterol and triglyceride metabolism [13].

Evidence suggests that adropin is expressed in various rat tissues with potential tissue specificity. In the brain, the immunoreactivity of adropin is present in the vascular area, pia matter, neuroglial cells, Purkinje cells, granular layer, and neurons of the central nervous system. In other tissues, adropin was detected in the glomerulus, peritubular interstitial cells, and peritubular capillary endothelial cells (kidneys), endocardium, myocardium, and epicardium (heart), sinusoidal cells (liver), and serous acini (pancreas). Tissue adropin levels based on mg/wet weight tissues were as follows: Pancreas > liver > kidney > heart > brain > cerebellar tissue. The data showed that the levels of adropin were higher in streptozotocin (STZ)-induced diabetic rats compared with the control rats [3]. However, the underlying mechanisms and potential effects remain to be further investigated.

Fish oil is a commonly used supplemental source containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), 2n–3 (v-3) polyunsaturated fatty acids (PUFAs) that have been shown to have a variety of protective effects against cardiometabolic diseases [15–17] It has been shown that a high-fructose diet in rhesus monkeys induces the features of MetS in humans, including obesity, dyslipidemia (particularly hypertriglyceridemia), and insulin resistance [18]. Administration of fish oil attenuates the decrease in circulating adropin concentrations in the monkeys [19], but the underlying mechanisms are unclear.

In humans, it was shown that serum adropin levels do not differ between males and females, and there is also no correlation between adropin levels and age. Similarly, it was reported that there is no gender difference between adropin levels in the pediatric age groups [20]. In normal-weight individuals, however, women have lower plasma adropin levels than men [21]. In addition, it was observed that adropin levels in male newborns are lower than those in the female. Cord blood adropin levels are positively correlated with gestational age and