Adropin – physiological and pathophysiological role

Adropina – rola fizjologiczna i patofizjologiczna

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Summary

Adropin is a peptide hormone that was discovered in 2008 by Kumar et al. This protein consists of 76 amino acids, and it was originally described as a secreted peptide, with residues 1-33 encoding a secretory signal peptide sequence. The amino acid sequence of this protein in humans, mice and rats is identical. While our knowledge of the exact physiological roles of this poorly understood peptide continues to evolve, recent data suggest a role in energy homeostasis and the control of glucose and fatty acid metabolism. This protein is encoded by the Enho gene, which is expressed primarily in the liver and the central nervous system. The regulation of adropin secretion is controversial. Adropin immunoreactivity has been reported by several laboratories in the circulation of humans, non-human primates and rodents. However, more recently it has been suggested that adropin is a membrane-bound protein that modulates cell-cell communication. Moreover, adropin has been detected in various tissues and body fluids, such as brain, cerebellum, liver, kidney, heart, pancreas, small intestine, endothelial cells, colostrum, cheese whey and milk. The protein level, as shown by previous research, changes in various physiological and pathophysiological conditions. Adropin is involved in carbohydrate-lipid metabolism, metabolic diseases, central nervous system function, endothelial function and cardiovascular disease. The knowledge of this interesting protein, its exact role and mechanism of action is insufficient. This article provides an overview of the existing literature about the role of adropin, both in physiological and pathophysiological conditions.

Key words: adropin • peptide hormone • Enho gene • carbohydrate-lipid metabolism • endothelium • cardiovascular diseases • diabetes

Introduction

Adropin is a peptide hormone which was discovered in 2008 by Kumar et al. during the microarray analysis of liver gene expression in mouse models of obesity. The name adropin was derived from the Latin words *aduro* (to set fire) and *pinquis* (fats or oils) [19]. Recent data suggest that adropin is a protein involved in energy homeostasis and the control of glucose and fatty acid metabolism [14,15,19]. However, our understanding of the exact physiological roles of this poorly understood peptide continues to evolve.

Levels of the protein in the circulation have been proposed to signal the metabolic state to muscle, influencing fuel selection preference to enhance glucose oxidation in the fed state [14,15]. Studies have shown that adropin regulates the expression of hepatic lipogenic genes and the PPARγ receptor (peroxisome proliferator-activated receptor gamma), the major regulator of lipogenesis [19]. Moreover, adropin influences angiogenesis, increases blood flow and capillary density in animal models of hind limb ischemia, and has a protective role for endothelial cells [22].

This article aims to provide general information on adropin and the role of this protein in the body of humans and animals.

Adropin — gene, expression, detection and concentration

Adropin was originally described as a secreted peptide, consisting of 76 amino acids with residues 1-33 encoding a secretory signal peptide sequence. The adropin amino acid sequence in humans, mice and rats is identical [19]. This protein is encoded by the Enho gene [19], which is located in mice chromosome 4 [24]. The Enho gene consists of two exons, while the open reading frame's (ORF) Enho gene is located in exon 2 [38]. Moreover, the Enho gene is located within quantitative trait loci (QTL) associated with obesity [24].

Expression of the Enho transcript has been described in the liver and brain [19,38]. Furthermore, it is believed that expression of Enho in the liver is regulated by the energy status and certain substances present in the diet [19]. Previous studies indicate that adropin is a protein associated with the cell membrane, with high expression in the brain (6-fold higher compared to the liver). Adropin, as a membrane-bound protein, can modulate cell-cell communication [38]. Adropin expression in the central nervous system may suggest that it has characteristics of a neuropeptide. Perhaps, this protein acts as an autocrine/paracrine factor on peripheral tissues [20]. However, there is no research confirming these hypotheses.

Currently there are no precise data indicating the molecular weight of this protein. Moreover, no data on the half-life of adropin have been reported.

While originally proposed to be a secreted peptide [19], more recently it has been proposed that adropin may be a membrane-bound protein [38]. Despite intensive research, the mechanism involved in the secretion of adropin is therefore controversial. The synthesis of adropin was initially found in the liver and brain of mice [19]. Probably adropin appears in other tissues and body fluids because it comes from the brain or the liver through the circulation system or from damaged cells. The protein secretion mechanism requires further research.

Adropin can be detected not only in the plasma and serum, but also in other body fluids, using commercial ELISA kits. The publications also present the immunohistochemical methods for detecting adropin in individual tissues (Fig. 1).

Adropin level changes in various physiological and pathophysiological conditions. The reduced concentration of adropin accompanies many diseases such as insulin resistance associated with obesity [8,19,29], gestational diabetes mellitus [10], non-alcoholic fatty liver disease [29], acute myocardial infarction [41] and endothelial dysfunction [9,16,39]. Low concentrations of adropin can be a risk factor for insulin resistance and other features of the metabolic syndrome, such as dyslipidemia [8]. Adropin concentrations in the blood are inversely correlated with BMI [8,9,41] and age [8]. Men have higher levels of adropin compared to women [8]. Average concentrations of adropin which are present in biological materials derived from humans and animals are presented in Table 1.

Adropin and carbohydrate-lipid metabolism

In the available literature concerning adropin, most attention is paid to its role in carbohydrate and lipid metabolism.

The pioneers in the field of animal adropin research are Kumar and colleagues [19]. This team not only discovered adropin and the Enho gene, but also demonstrated that expression of the Enho gene in the liver varies depending on the diet. In case of mice with diet- and/or genetically induced obesity, reduction in adropin gene expression is observed. Overexpression or systemic administration of adropin to mice with diet-induced obesity (DIO) reduces liver steatosis and insulin resistance.

Another study of Kumar et al. [20] was focused on understanding how adropin deficiency influences the phenotype of adropin-deficient mice and metabolic homeostasis. The serum concentrations of adropin in chow-fed conditions were significantly higher compared to the fasting levels. Also in diet-induced obesity adropin concentrations were lower. Diet, especially its fat content, affected concentrations of this protein. Mice which are on a high fat diet with a lower carbohydrate intake had a higher level of serum adropin than mice which remained on a low-fat diet with a high intake
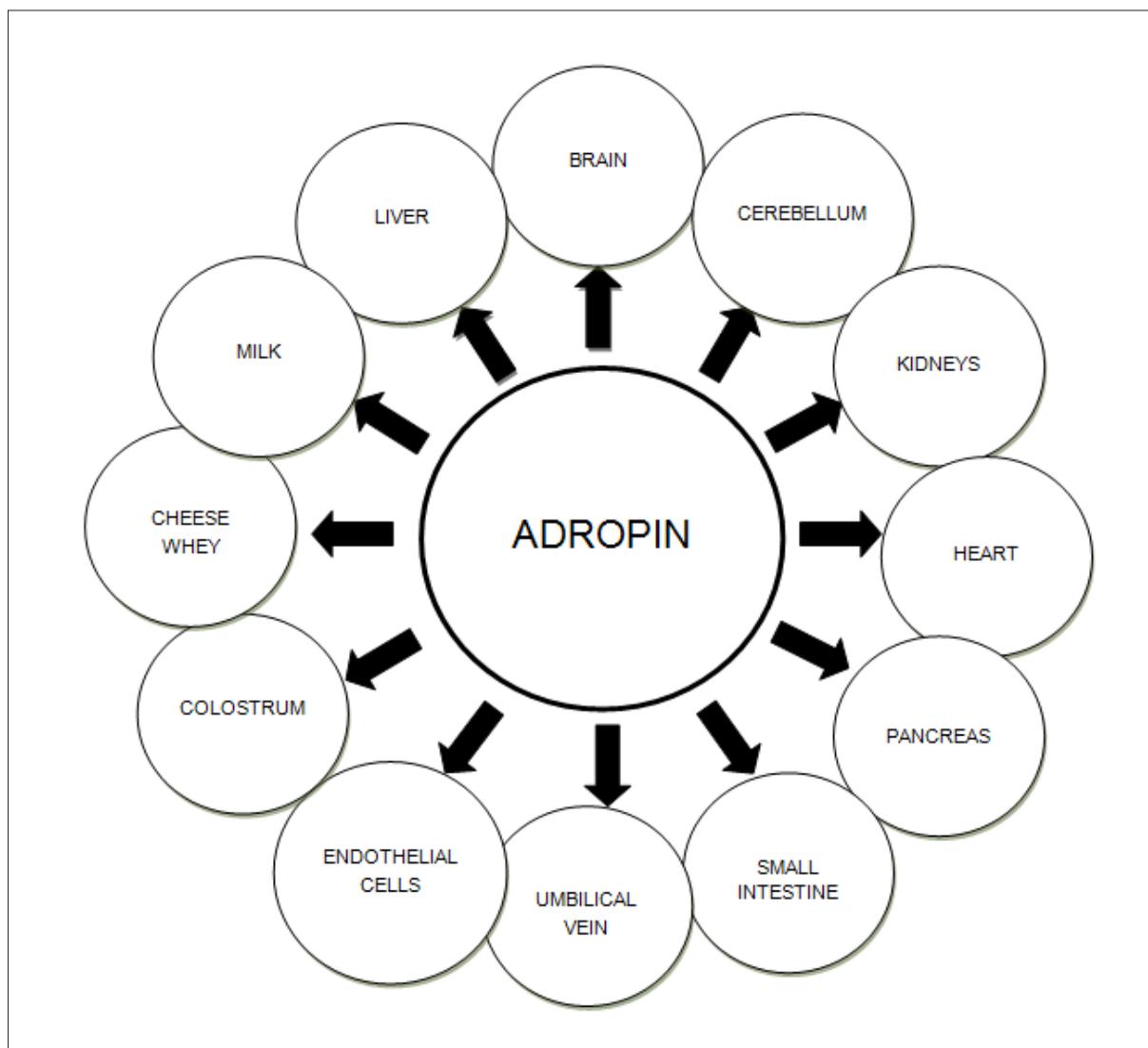
Fig. 1. Adropin in tissues and body fluids [2,3,4,5,19,22]

of carbohydrates. In order to demonstrate the participation of adropin in metabolic homeostasis, Kumar et al. [20] analyzed AdrKO deficient mice (adropin knock-out). In these mice an increase of obesity was observed, despite maintaining normal food intake and energy consumption. In addition, in these mice dyslipidemia, dysregulation of endogenous synthesis of glucose and finally insulin resistance were present. Adropin concentrations are regulated by the supply of macronutrients, and their increase is associated with a high content of fat in the diet. Despite the lack of effect on the regulation of appetite, adropin participates in the regulation of carbohydrate and lipid metabolism.

Based on previous research, it was found that adropin plays an important role in the regulation of metabolic homeostasis, especially glucose and fatty acids [14,15]. The first study focused on the content of protein substrate oxidation preferences in skeletal muscle, in the cycle of feeding and fasting. It was found that adropin strongly promotes the oxidation of carbohydrates, rather than fatty acid, in adropin knockout and transgenic mice [14]. The second study pointed to the role of adropin as a physiological regulator of glucose and fatty acid oxidation. It was found that DIO mice treated with adropin[34-76] exhibited increased glucose tolerance, improved insulin resistance and promotion of carbohydrates in oxidation reactions [15].

Aydin et al. [4] studied the expression of adropin in the rat brain, cerebellum, kidney, heart, liver and pancreas in rats with streptozotocin (STZ)-induced diabetes. In comparison to control animals, rats with STZ-induced diabetes presented higher adropin levels in both the serum and in tissues.

Lifelong caloric restriction in mice affects the degree of metabolic adaptation, characterized by reduced lipogenesis, increased lipolysis and ketogenesis. The study also

Table 1. The concentration of adropin in biological materials

Type of biological material	The source of biological material	Concentration of adropin	References
BLOOD	Women	3,0 ng/ml	[8]
	Men	4,1 ng/ml	[8]
	Adults with normal weight	3,4 + 1,8 ng/ml 4,1 ng/ml 5,12 + 1,44 ng/ml 6,0 + 0,3 ng/ml	[9] [8] [41] [21]
	Overweight adults	3,3 ng/ml	[8]
	Adults with obesity	2,7 ng/ml	[8]
	Adults with type 2 diabetes	4,67 + 1,43 ng/ml	[12]
	Adults with type 2 diabetes and endothelial dysfunction	3,04 + 0,79 ng/ml	[12]
	Healthy pregnant women	3,3 + 1,3 ng/ml	[10]
	Pregnant women with GDM	2,4 + 2,0 ng/ml	[10]
	Children	7,4 ng/ml	[16]
	Rats	21,66 + 4,06 ng/ml	[5]
	Cows	3,00 + 0,43 ng/ml	[2]
UMBILICAL CORD BLOOD	Preterm newborns	1413-2484 pg/ml	[26]
	Term newborns	1960-2684 pg/ml	[26]
	Newborns of healthy mothers	3,3 + 1,3 ng/ml	[10]
	Newborns of mothers with GDM	1,5 + 0,9 ng/ml	[10]
MILK	Human	9-14,5 ng/ml	[3]
	Cows	5,0 + 1,11 ng/ml	[2]
CHEESE WHEY	Cows	5,13 + 0,57 ng/ml	[2]

demonstrated the presence of significant changes in fat metabolism in the liver. Moreover, adropin gene expression was significantly increased, which explains the decrease in lipogenesis in tested animals. The increase in the concentration of adropin, with lifelong caloric restriction, may protect the liver from fat accumulation aggravating with age [18].

Nonalcoholic fatty liver disease (NAFLD) is a chronic liver disease, manifested by excessive fat accumulation,

which is not caused by alcohol. This disease is linked to obesity, insulin resistance and type 2 diabetes [1,29]. The concentration of adropin in obese patients with NAFLD is much lower in comparison to patients without NAFLD, or to healthy controls. Low concentrations of adropin can therefore be considered as an independent risk factor for NAFLD in obese people. Evaluation of the protein concentration is a reliable indicator of hepatic steatosis in patients with obesity [29].

The first evidence indicating a link between adropin, obesity and the risk of metabolic syndrome in humans was presented by Butler et al. [8]. The study was conducted on plasma samples of male and female volunteers, which were obtained from five separate studies from many centers. It was found that a reduced concentration of adropin accompanied obesity and insulin resistance and that weight loss increased the level of adropin. There were no diurnal fluctuations and/or changes in the concentration of adropin between meals. Its levels decreased with age, and lower concentrations were accompanied by the presence of two or more risk factors of the metabolic syndrome, regardless of gender.

Gestational diabetes mellitus (GDM) is a disorder of glucose tolerance, manifested during pregnancy. GDM occurs most frequently in those women who have abnormal endogenous insulin production, or in women with symptoms of insulin resistance before pregnancy. In addition, GDM is diagnosed in pregnant women who had diabetes before pregnancy [17]. GDM is a condition characterized by increased insulin resistance and beta-cell inability to compensate for increased level of insulin resistance [27]. When it is uncontrolled, it can cause serious complications for the mother, fetus and newborn [7,27]. It has been identified that women with GDM have a decreased plasma level of adropin and increased glucose concentration. In contrast, in cord blood derived from women with GDM lower adropin concentrations were accompanied by lower concentrations of glucose. At the same time, adropin levels in cord blood were negatively correlated with maternal age, fasting insulin level, HOMA-IR (homeostasis model assessment of insulin resistance) and birth weight. However, no correlation with the concentration of adropin in maternal blood was observed [10].

Yildirim et al. [40] examined the relationship between serum concentrations of adropin and metabolic parameters in women with polycystic ovary syndrome (PCOS). PCOS is an endocrine disease. As in the case of metabolic syndrome, a major cause of its occurrence is insulin resistance and compensatory hyperinsulinemia [31]. In women with PCOS, the researchers found a significantly lower level of adropin compared to healthy women. In addition, in patients with PCOS the concentration of adropin is negatively correlated with serum levels of insulin, cholesterol and triglycerides, as well as HOMA-IR [40].

St-Onge et al. [32] evaluated the association between plasma levels of adropin and the duration of sleep and dietary preferences. It has been shown that the reduction of sleep to 4 hours per day did not affect plasma levels of adropin. The concentration of this protein correlates with dietary preferences and in particular with the intake of fat, regardless of the time spent sleeping.

ADROPIN AND CENTRAL NERVOUS SYSTEM

In connection with the detection of adropin in the brain, the potential role of this protein in the central nervous system is very interesting. Expression of the Enho gene in the brain takes place in those areas which are involved in the regulation of metabolism [19]. Wong et al. [38] reported that the content of adropin in the brain is the highest and, in addition, it shows an interaction with NB-3/contactin 6 (cerebrospinal specific ligand). NB-3 is a functional ligand of Notch1 [11], and it shows high expression in the cerebellum after birth [33]. Knockout of the adropin gene in mice resulted in decreased physical activity and abnormal coordination and motor activity in animals, in combination with impaired formation of synapses in the cerebellum. Similar results were observed in the absence of NB-3, a protein that is essential for proper development of the mice cerebellum [28]. These results indicate a link between adropin and NB3 protein. Interactions between these two proteins by the signaling pathway NB-3/Notch are essential for normal motor activity and coordination, as well as for the proper development of the cerebellum [38]. It is necessary to know the exact molecular mechanisms of adropin action in the area of the brain.

ADROPIN AND ENDOTHELIUM

Endothelium plays an important role in maintaining vascular homeostasis. The endothelium is often referred to as the largest endocrine organ [23]. Endothelial cells synthesize and secrete a number of biologically active substances [6]. The endothelium is important for maintaining a balance between factors regulating expansion and narrowing of the vessel [37]. The most active vasodilator produced by endothelial cells is nitric oxide (NO). Its synthesis occurs in a continuous manner from the amino acid L-arginine by nitric oxide synthase (NOS) [35]. Changes in the endothelium are associated with a reduced effect of nitric oxide, resulting from the loss of its generation or absence of biological activity [36]. One of the factors that affect endothelial function and eNOS (endothelial nitric oxide synthase) activity is adropin [30]. It was reported that this protein is a marker indicating endothelial dysfunction in patients with type 2 diabetes [34].

In order to assess the vascular effects of adropin, the researchers used in vitro cell culture models combined with a defective in vivo murine model. Endothelial cells treated with adropin showed enhanced proliferation, migration and arrangement of the shape of a capillary-like tube. Furthermore, they presented lower permeability and apoptosis induced by TNF-α. It was also found

that adropin influences gene expression of endothelial nitric oxide synthase (eNOS) by the VEGFR2-phosphatidylinositol 3-kinase-Akt and VEGFR2-extracellular signal regulated kinase 1/2 pathways, thereby regulating the bioavailability of nitric oxide [22].

Obstructive sleep apnea (OSA) is a disorder characterized by repeated episodes of upper respiratory tract obstruction, which leads to apnea and/or hypopnea [12]. OSA adversely influences the function of many organs and body systems. It is believed that OSA is an independent risk factor for cardiovascular disease and endothelial dysfunction [12]. Previous studies have indicated that obstructive sleep apnea was accompanied by decreased adropin levels, but only if it was also accompanied by impaired endothelial function. Therefore, results of research confirmed that the assessment of adropin concentration is a reliable indicator of endothelial dysfunction in patients with OSA [16].

ADROPIN AND BIOLOGICAL FLUIDS

Blood concentration of adropin was determined not only in the plasma/serum. The presence of adropin (and other peptides such as ghrelin, nesfatin-1, apelin-12 and salusin) was measured in plasma, cheese whey and in milk of dairy cows [2]. It was found that the concentration of cheese whey adropin is almost two-fold higher than in blood plasma, but only slightly higher than in milk. The concentration of the other tested peptides in milk and cheese whey was 1.3-1.4 times higher than in plasma. This may suggest that these proteins diffuse or are actively transported from the blood into milk, or can be synthesized by the mammary gland.

Another study was focused on measuring the adropin content in women's breast milk [3]. Milk samples were derived from lactating women with or without GDM and non-lactating women. In healthy women adropin concentration was the highest in colostrum, lower in transitional milk, and the lowest in mature milk. In women with GDM, adropin concentrations in colostrum and transition milk were significantly lower than in mature milk.

ADROPIN AND NEWBORNS

The association between adropin concentrations in cord blood and human fetal growth parameters was studied by Qiu et al. [26]. This study showed that adropin concentrations in cord blood of preterm newborns (PN) were significantly lower than in the term delivery group (TD). The TD group showed no significant correlation between serum adropin levels and fetal growth parameters. In contrast, the concentration of this peptide hormone was positively correlated with gestational age at birth and placenta weight. In the PN group no correlation with placenta weight was observed. Furthermore, in this group lower adropin levels in male newborns were detected.

ADROPIN AND CARDIOVASCULAR DISEASE

There are more and more reports indicating the involvement of adropin in the functioning of the cardiovascular system. As mentioned previously, the immunoreactivity of adropin has been detected in many tissues, including the heart [4].

The potential participation of adropin in the processes associated with myocardial infarction (MI) is very interesting. In an animal study, myocardial infarction was induced by administration of isoproterenol, and the authors evaluated adropin content in the heart. In addition, further parameters were measured, including adropin, troponin-1, creatine kinase and CK-MB in serum. Adropin synthesis in the hearts of rats affected by myocardial infarction was higher than in the control group. In addition, serum concentrations of this protein increased at 30 minutes after a heart attack and peaked at 2 hours. When myocardial cells become damaged, adropin is released into the bloodstream. However, there was a positive correlation between the concentrations of adropin and troponin-1 [5].

Adropin deficiency may play an important role in the development and progression of acute myocardial infarction (AMI), because the concentrations of adropin in serum were significantly lower in patients with AMI compared to patients with stable coronary artery disease and healthy persons. This protein is an independent early predictor of AMI in patients with coronary artery disease [41].

In addition, studies have shown that a lower concentration of adropin is a risk factor for the development of coronary heart disease [42] and an independent factor for late saphenous vein graft occlusion [13]. However, adropin level increases with severity of heart failure [21].

Cardiac syndrome X (CSX) raises a lot of controversies regarding its classification, pathogenesis, prognosis and treatment. CSX is suspected in patients with pain sensations that are likely to be of coronary nature, who have a positive electrocardiographic exercise test, and with no changes in the epicardial coronary arteries in angiography [25]. It is known that one of the reasons for CSX is endothelial dysfunction [9]. It was suspected that adropin may play a significant role in the pathophysiology of CSX. The first study on the relationship between adropin and CSX showed that low circulating levels of adropin are associated with this disease and concentrations less than 2.73 ng/ml predispose to the development of CSX. Higher levels of adropin protect the endothelium, prevent insulin resistance and improve glucose tolerance [9].

CONCLUSION

This article demonstrates the correlation between the adropin level and various physiological and pathophysiological states, both in humans and animals. Adropin

is a hormone which is not yet completely understood. Currently, it is known that it probably plays a role in metabolic processes. This protein plays an important role in glucose and fatty acid homeostasis. Moreover, the discussed studies indicate the involvement of adropin in carbohydrate-lipid metabolism, metabolic diseases, endothelial function and cardiovascular disease. It is necessary to know the exact molecular mechanisms of adropin action in the area of specific tissues,

in specific diseases or physiological states. Individual studies which report adropin's role in physiological and pathophysiological processes should be confirmed. In view of the identical amino acid sequence in humans and mice, conclusions from animal studies can be applied to humans. A thorough knowledge of adropin's action will probably enable this protein to be used for therapeutic purposes in the case of various metabolic disorders.

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