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The role of the apelinergic and vasopressinergic systems in the regulation of the cardiovascular system and the pathogenesis of cardiovascular disease

Katarzyna Czarzasta, Agnieszka Cudnoch-Jedrzejewska

Department of Experimental and Clinical Physiology, Medical University of Warsaw, Warsaw, Poland

INTRODUCTION

The incidence rate of cardiovascular disease (CVD) is currently very high, particularly among obese subjects. Despite advances in medicine, the pathogenesis of many CVD has not been entirely clear. Recently, particular attention has been paid to concurrent occurrence of abnormal regulation of feeding and CVD in people subjected to chronic stress or depression. Multiple studies seem to confirm that obesity and stress are among major risk factors for CVD [1]. Unfortunately, the number of obese subjects in the developed countries is rapidly rising. The main cause of obesity is excessive food intake, and particularly high-fat products. Increased food intake was shown to affect adipocyte proliferation, leading in turn to an increase in body mass. In the recent years, the adipose tissue was found to be a source of biologically active substances known as adipokines, including apelin (AP), that may play an important role in the regulation of the cardiovascular system. Preproapelin mRNA and protein was identified, among others, in the paraventricular nucleus (PVN) and the supraoptical nucleus (SON) in the hypothalamus, both being the major sites producing arginine vasopressin (AVP) which takes part in the central regulation of blood pressure. AVP was also shown to affect feeding and response to stress [1]. Recent studies indicate a role of AP in the central regulation of blood pressure, with varied effects in rats fed a high-fat diet and subjected to chronic stress compared to non-stressed animals receiving a standard diet [2].

In the recent years, multiple studies have also been published that show an important contribution of the apelinergic and vasopressinergic systems and their interactions in the pathogenesis of CVD [3]. AVP receptor antagonists (vaptans) have been introduced for the treatment of patients with chronic heart failure (CHF) and hyponatraemia. Studies are underway to evaluate the possibility of AP analogue use in the management of patients with ischaemic heart disease [4, 5].

The purpose of this paper is to review the literature on the role of the apelinergic and vasopressinergic systems in the regulation of the cardiovascular system and the pathogenesis of CVD.

APELINERGIC SYSTEM

Apelin is a biologically active peptide from the adipokine family, occurring in several isoforms that are agonists of an orphan AP receptor (APJ) [6]. High biological activity is mostly exhibited by apelin-36, apelin-17, and apelin-13, all formed from their precursor preproapelin (Fig. 1). The presence of AP and its receptors was identified both in brain and in peripheral organs and tissues including the heart, blood vessel, and the adipose tissue [7].

APELIN AND THE CARDIOVASCULAR SYSTEM

In vitro and *in vivo* studies showed a positive inotropic effect of AP, likely due to activation of myosin light chains [7, 8]. A vasodilatory effect of peripherally administered AP was observed in experimental and clinical studies. No such clear results, however, were obtained in studies regarding central regulation of the cardiovascular system [9].

Studies increasingly indicate a role of the apelinergic system in the pathogenesis of CVD. The apelinergic system was shown to contribute to the development of hypertension, ischaemic heart disease, and CHF. In spontaneously hypertensive rats, an increased expression of apelin mRNA and protein was noted in the rostral ventrolateral medulla, an area participating in the regulation of the cardiovascular system, along with decreased expression of AP and APJ receptors in

Address for correspondence:
Agnieszka Cudnoch-Jedrzejewska, MD, PhD, Department of Experimental and Clinical Physiology, Medical University of Warsaw, ul. Pawińskiego 3c, 02–106 Warszawa, Poland, e-mail: agnieszka.cudnoch@wum.edu.pl

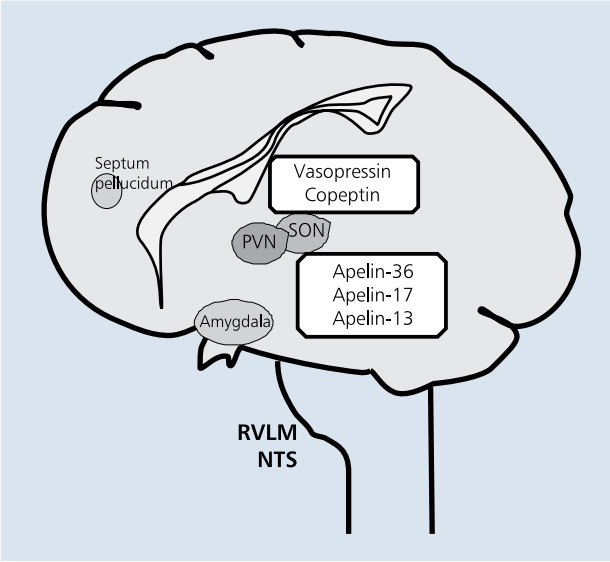

Figure 1. Biologically active peptides of the apelinergic and vasopressinergic systems synthesized in the hypothalamus; PVN — paraventricular nucleus; SON — supraoptical nucleus; RVLM — rostral ventrolateral medulla; NTS — nucleus tractus solitarii

the myocardium and the aorta [10, 11]. Reduced plasma AP level was found in patients with essential hypertension [12].

In mice with CHF, peripherally administered AP prevented myocardial fibrosis by reducing alpha-smooth muscle actin activity [13]. Changes in plasma AP level related to disease severity were reported in patients with CHF. Patients with New York Heart Association (NYHA) class I and II heart failure demonstrated higher plasma AP levels compared to those with NYHA class III and IV heart failure. It was shown, however, that changes in plasma AP level in patients with CHF are less significant compared to changes in classical biomarkers such as N-terminal pro-B-type natriuretic peptide (NT-proBNP) and tumour necrosis factor-alpha, which is an important limitation of these measurements [14, 15].

The most recent studies also seem to confirm a beneficial effect of AP on the myocardium in the setting of an acute myocardial necrosis. In rats with myocardial infarction, a cardioprotective effect of AP was shown, resulting from activation of nitric oxide synthase and reduced activity of lactate dehydrogenase, creatinine kinase MB isoenzyme, and malonyldialdehyde [16]. In a murine model of myocardial infarction, AP was shown to participate in the activation of neovascularisation on the first day after the acute event, a process leading to improved myocardial perfusion, reduced scar extent, and increased survival [17].

APELIN AND OBESITY

Sawane et al. [18] showed a potential for the use of AP in the treatment of diet-induced obesity. Evidence are also available that indicate a direct effect of AP on food intake which likely depends on fat content of the diet. In rats on a high-fat diet, AP did not reduce appetite, while it reduced food intake in animals fed standard diet and in fasting conditions [19]. Multiple experimental and clinical studies indicate an association between AP and insulin, one of the most important hormones that regulate metabolism [20]. Although expression of AP mRNA in the adipose tissue and plasma AP level were shown to be more strongly related to plasma insulin level than to the presence of obesity [21], body mass reduction by the use of a low-calorie diet in subjects with elevated body mass index resulted in reduced plasma AP level and reduced AP mRNA content in the abdominal adipose tissue [22].

Recent studies suggest a role of AP in the regulation of the cardiovascular system also in obesity. In an *in vitro* study in cultured cardiomyocytes, Ceylan-Isik et al. [23] showed that AP increased cardiomyocyte contractility when added to the culture medium. In mice fed a high-fat diet, the same authors noted that intraperitoneal administration of AP prevented myocardial hypertrophy and resulted in an improved systolic function of the myocardium. Czarzasta et al. [24] reported no central pressor effect of AP both in rats fed a high-fat diet and in rats with post-infarction heart failure.

APELIN AND STRESS

Few studies indicate an association between apelin and stress. Increased APJ receptor mRNA expression in PVN was noted in Wistar rats subjected to acute or chronic stress [25]. The presence of APJ receptor mRNA and AP protein in PVN and the pituitary gland suggests its role in the release of adrenocorticotropic hormone (ACTH) and corticosterone, likely via an AVP-related mechanism involving the V1b receptor [26].

THE VASOPRESSINERGIC SYSTEM

The major sites of AVP synthesis are PVN and SON, where AVP is synthesized from provasopressin which a precursor for also another vasopressinergic system mediator, copeptin (Fig. 1). It seems that the main function of copeptin is its role in the transport of AVP-containing neurosecretory vesicles from the hypothalamus to the posterior pituitary where AVP is released into the bloodstream [27]. AVP and probably also copeptin act on target organs and tissues via vasopressinergic V1 and V2 receptors. V1 receptors are located mainly in the brain but also in peripheral tissues and organs including the heart and blood vessels, and V2 receptors are located mostly in the kidney [28].

VASOPRESSIN AND THE CARDIOVASCULAR SYSTEM

Vasopressinergic neurons are located in many central nervous system areas that participate in blood pressure regulation [29]. It has been long established that AVP exerts a pressor effect [1].

In addition, multiple studies indicate a role of AVP in the pathogenesis of CVD. An increased activity of the vasopressinergic system was reported in animal models of hypertension and post-infarction heart failure [30, 31]. In contrast, Nazari et al. [32] showed a cardioprotective effect of AVP via V1 receptors. Lanafear et al. [33] reported an association between increased plasma AVP level and increased mortality among patients with CHF.

Recently, much hope has been placed on another vasopressinergic system peptide, copeptin, as a potential marker of CVD progression. Of note, plasma copeptin is much more stable compared to AVP, and its level does not change in relation to age [34].

Clinical studies indicate a strong correlation between copeptin and the degree of myocardial damage in patients with CHF [35]. Neuhold et al. [36] showed a superior prognostic value of plasma copeptin levels in patients with advanced heart failure as compared to conventional biomarkers such as BNP and NT-proBNP. Kelly et al. [37] reported a negative correlation between plasma copeptin level and left ventricular ejection fraction.

VASOPRESSIN AND OBESITY

The presence of vasopressin V1 receptors in brown adipose tissue suggests the latter may play an important role in the regulation of body mass and metabolism [38]. In the recent years, it has been shown that vasopressin, acting via central V1 receptors, inhibits food intake which may limit the development of obesity. Currently, a subject of intensive research is the effect of AVP on glucose metabolism. A significant impairment of glucose tolerance was noted in mice lacking V1a receptors, while those lacking V1b receptors showed improved glucose tolerance [39]. Improved glucose tolerance was also seen in rats with genetic AVP deficiency, secondary to a lack of ligands for both types of AVP receptors [40]. Metabolic disturbances were also reported in human subjects carrying the T allele of the V1 receptor gene who consumed high-fat meals [41]. Enhörning et al. [42] found an association between high plasma copeptin levels and the development of abdominal obesity, metabolic syndrome, and diabetes.

VAZOPRESSIN AND STRESS

Numerous studies, both experimental and clinical, showed an increased activity of the vasopressinergic system during stress, including elevated plasma AVP level [43]. AVP, released together with corticotropin-releasing hormone to the hypophyseal portal system, plays an important in the regulation of ACTH release, with the latter hormone stimulating glucocorticosteroid release [44]. Our own observations indicate a role of central V1 receptors in the potentiation of cardiovascular system response to acute stress both in animals with myocardial infarction and those subjected to chronic stress [30, 45].

RELATIONS BETWEEN THE APELINERGIC AND VASOPRESSINERGIC SYSTEMS

Preproapelin mRNA and protein were detected, among others, in PVN and SON in the hypothalamus which are also the main sites of AVP synthesis [46], suggesting a role of apelin in the regulation of vasopressinergic neuron activity (Fig. 1). This hypothesis seems to be supported by electrophysiologic studies that showed an effect of apelin on the activity of SON neurons [47]. Intraventricular administration of apelin reduced vasopressinergic neuron activity and resulted in decreased plasma AVP level [46]. An imbalance between the apelinergic and vasopressinergic systems was also observed in patients with CHF [48].

SUMMARY

Research studies indicate a role of the apelinergic and vasopressinergic systems both in the regulation of the cardiovascular system and the pathogenesis of CVD, including in such settings as obesity and stress. Based on these data, it may be suggested that interactions between these systems underlie numerous physiological and pathophysiological processes, some of them related to the cardiovascular system. Better understanding of the role of these systems and their interactions, both physiological and related to the pathogenesis of CVD, will allow further advances in prevention and drug therapy.

Conflict of interests: *none declared*

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