Invited critical review

Apelin in acute myocardial infarction and heart failure induced by ischemia

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Abstract

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Apelin is a recently isolated novel endogenous ligand for the angiotensin-like 1 receptor (APJ). Initial experiments in animal models indicate that the cardiovascular system is the main target of the apelin–APJ system. Apelin plays an opposite role to the renin-angiotensin-aldosterone system as a compensatory mechanism. It is reduced in patients with heart failure, also of ischemic origin. However, only animal studies concern the role of the apelin–APJ system in myocardial ischemia. Less is known about the function of this adipokine in an acute phase of myocardial infarction in human. The apelin–APJ system could perhaps be involved in myocardial protection during acute myocardial ischemia. In the current review we have summarized recent data concerning the role of apelin in acute myocardial infarction and heart failure induced by ischemia.

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1. Introduction

Apelin belongs to the adipokines — a term used to denote cytokines, growth factors, and other proteins produced and secreted by adipocytes. These factors are also called adipocytokines [1]. This does not imply that expression and production of such factors is restricted to adipocytes as most of these factors are also produced by a variety of other cell types. The term often refers to leptin and adiponectin, which are secreted by the adipocytes of adipose tissue. A variety of other factors are also released by adipose tissue in vitro and in vivo and these have been also termed collectively as adipokines or adipocytokines (TNF-alpha, IL-6, leptin, omentin, visfatin, adipasin, resistin, apelin, retinol binding protein rbp4) [2].
and it is widely expressed in various tissues and cell types [6], Fig. 1. Apelin-36 is a 36-amino acid C-terminal fragment of the preproapelin and was first characterized as endogenous APJ receptor ligand, but several smaller C-terminal peptides were shown to be even more potent in activating APJ. Shorter synthetic C-terminal peptides consisting of 13 to 19 amino acids were found to exhibit significantly higher activity than apelin-36 [5,7], whereas the most effective pyroglutamylated form is apelin-13 [5], Fig. 1.

Apelin—APJ system is expressed in the central nervous system and periphery [8] with a role in the regulation of fluid and glucose homeostasis, feeding behavior, vessel formation, cell proliferation and immunity [9], Fig. 2. In magnocellular neurons of the hypothalamus, apelin is upregulated by dehydration through a mechanism that may involve arginine vasopressin [10]. However, the evidence indicates that the cardiovascular system is the main target of apelin. Based on some results, it can be anticipated that apelin, like angiotensin II, may have an important role in the regulation of cardiovascular homeostasis [6]. Apelin is one of the most powerful endogenous positive inotropic substances [11], Fig. 2. In addition to the inotropic effects of apelin, several mechanisms have been described whereby apelin regulates vascular tone and blood pressure. Intravenous injection of apelin lowers blood pressure by triggering the release of nitric oxide from endothelial cells [12] and reduces water and sodium uptake in the kidneys by inhibiting vasopressin discharge [13]. Moreover, it has diuretic properties [13]. Apelin plays a primary role in countering angiotsin-induced vasoconstriction [14].

There is some animal data suggesting that the apelin—APJ system might be an important regulator of vascular function in diabetes [15], Fig. 2. Animal and human data suggest that apelin production is enhanced in obesity and could help to understand potential links between obesity and associated disorders such as inflammation and insulin resistance [16,17]. In adipocytes, apelin gene expression is inhibited in the fasting state and stimulated by refeeding possibly through changes in the plasma concentrations of insulin and counter-regulatory hormones [17].

Apelin is present in human plasma and myocardium. Apelin mRNA levels increase in left ventricle in chronic heart failure due to coronary heart disease and dilated cardiomyopathy [18]. Moreover, apelin plasma levels are reported to increase especially in the early stage of left ventricular dysfunction [19].

However, the majority of studies regarding apelin have been provided on animal models; little is known about its function in human. The current review is devoted to the role of apelin in acute myocardial infarction and ischemic heart failure.

3. Apelin expression in acute hypoxia and myocardial infarction

3.1. Animal studies

The majority of experimental data regarding the role of apelin in cardiovascular system has been conducted in rodents. Sparse studies used other animals. Del Ry et al. have been used a wild boar (Sus scrofa) model to establish its genoma sequence for apelin for future applications of molecular biology studies [20]. While other researchers, on the canine model, have investigated the influence of apelin on changes in intracellular sodium current, which may contribute to the apelin inotropic effects [21].

Regulation of the apelin—APJ pathway is altered by acute ischemic injury. Ronkainen et al. for the first time have demonstrated that hypoxia regulates apelin gene expression and secretion in cardiac myocytes [22]. Hypoxic induction of apelin could be a part of the acute response of the heart muscle to an impaired oxygen supply, such as at the time of myocardial infarction. Myocardial gene expression as well as secretion of apelin are activated by hypoxia via activation of hypoxia-inducible factor-1 (HIF-1). This factor is also responsible for regulation of expression of several hypoxia-inducible genes including erythropoietin, adrenomedullin and heart-specific atrial natriuretic peptide [23–25]. Sheikh et al. in the murine model investigated influence of heart failure induced by ischemia on apelin—APJ pathway expression in the heart muscle, lung and skeletal muscle [26]. The authors found in vivo and in vitro experiments that apelin and APJ are markedly upregulated following ischemia and hypoxia via HIF-2α pathway. They were able to demonstrate that this effect is restricted particularly to the postarterial [capillary and venous] endothelium. Apelin and APJ mRNA expression progressively increased by consecutive weeks following ischemic injury. Accordingly, apelin expression is upregulated in vivo within 24 h of myocardial infarction. Endogenous cardiac apelin and APJ are increased in rats with ischemic heart failure 6 weeks postmyocardial infarction [27]. Moreover, infusion of apelin-13 significantly enhanced myocardial function in failing hearts. Thus, the total myocardial apelin and APJ receptor levels increase in compensation for ischemic cardiomyopathy. It is not clear whether the stimulus for this upregulation is ischemia or the early onset of heart failure. In contrast, both apelin and APJ expression fell in a further rodent model of ischemic myocardial injury caused by repeated isoproterenol administration [28]. However, it must be noted that this model produced extensive myocardial injury and very severe heart failure associated with hypotension and grossly elevated left ventricular end-diastolic pressure. Interestingly, while cardiac APJ mRNA levels were markedly downregulated in these rats, both tissue levels and overall apelin-binding capacity of APJ within the heart were increased. This might reflect either more efficient posttranscriptional processing of APJ or diminished breakdown of existing APJ receptors, with or without a contribution from enhanced receptor recycling. In myocardium with a limited oxygen supply, increased apelin expression could therefore serve as an adaptive mechanism to maintain the contractile function of the heart. It has been shown that overexpression of HIF-1α reduced infarct size and limited the progression of infarct-induced cardiac failure in mouse

![Fig. 1. Apelin synthesis and metabolism (based on Japp A.G. and co-workers).](image-url)
Thus, as a consequence of being a HIF target gene, apelin might well play a part in the early events protecting the heart against hypoxia-induced damage raising the possibility of using apelin as a therapeutic agent for ischemic heart failure patients. Kleinz et al. have showed that in ischemic myocardium of isolated rat hearts apelin mRNA is upregulated, but returns back to baseline after reperfusion [30]. Therefore the authors have suggested that apelin or a pharmacological agonist of APJ receptors could act as novel approaches for attenuating myocardial ischemia and reperfusion injury in patients with coronary artery disease. Recent interesting experimental data have indicated that the expression of the apelin—APJ pathway during differentiation of bone marrow mononuclear cells (BMSCs) into cardiomyogenic cells may be an important mechanism in regulation of myocardial regeneration and its functional recovery after acute myocardial infarction [31].

Thus, increasing evidence from pre-clinical models has suggested that apelin—APJ signaling mediates important effects on hypoxia and ischemia. However, the data provided with human studies seem to be limited.

3.2. Human studies

Studies concerning the role of apelin in AMI in humans are scarce. In humans the majority of studies have been conducted in vivo. However, Pitkin et al. have performed an investigation on human tissues (cardiomyocytes as well as coronary artery and epicardial adipose tissues), which were collected were from patients undergoing cardiac transplantation for dilution cardiomyopathy or ischemic heart disease, or from control hearts from donors where there was no suitable recipient [32]. They have found changes in the apelin/APJ system in human diseased cardiac and vascular tissue. Apelin was upregulated in human atherosclerotic coronary arteries and potently constricted vessels. On the other hand, they found the decrease in APJ receptor density in heart failure, which may limit the positive inotropic actions of apelin, contributing to contractile dysfunction. In vitro model was also used to discover that apelin is a novel insulin-regulating islet peptide in humans as well as several laboratory animals [33].

It is known that exogenous apelin has acute and chronic positive inotropic effects in the myocardium [11,34,35]. In man in vivo it has been shown that acute apelin administration causes NO-mediated arterial vasodilation, but does not appear to affect peripheral venous tone [36]. Our previous studies provided information that in low risk ST-elevation myocardial infarction patients, treated with primary percutaneous coronary intervention (pPCI) and with preserved left ventricle ejection fraction (LVEF) the decrease of plasma apelin concentrations could be found in the first five days after the onset of myocardial infarction [37]. This reduction was independent of the degree of LV dysfunction and prognosis [38]. Weir et al. in patients with acute myocardial infarction (AMI) and low LVEF confirmed our results: plasma apelin concentration was lower in patients with AMI in comparison with the control group early after infarction and persisted low over time [39]. Apelin concentration did not correlate with any parameter of LV. Interesting results were brought by Kadoglou et al. [40]. A total of 355 participants were enrolled into the KOZANI Study. Among them there were 80 patients with unstable angina (UA) and 115 patients with acute myocardial infarction (AMI) hospitalized in the coronary care unit. Apelin concentrations were lower in coronary artery disease (CAD) patients as compared to controls. UA and AMI groups had lower apelin levels on admission compared with the asymptomatic CAD group. Moreover, apelin concentrations were inversely associated with the severity and the acute phase of CAD, which suggests its involvement in the progression and destabilization of coronary atherosclerotic plaques. Similar results were obtained by Li et al. [41]. Reduced apelin levels were observed in this homogenous population of stable angina subjects and the plasma apelin level was negatively correlated with the degree of coronary stenosis as measured by Gensini score.

4. Apelin and ischemic heart failure

4.1. Animal studies

The role of apelin—APJ in the pathogenesis of heart failure has received a great attention. Szokodi et al. were the first group to report downregulation of apelin mRNA in cardiac myocytes under cyclic stretch in vitro and in ventricular myocardium from two rat models of hypertensive heart failure [11]. In animal models of heart failure the expression of apelin and APJ is increased or maintained in animals with left ventricular hypertrophy and compensated heart failure, but downregulated in those with severe, decompensated heart failure. This could be due to cardiac dilatation in advanced heart failure, which may contribute to downregulation of the apelin—APJ system since cardiomyocytes subjected to mechanical stretch in vitro exhibit markedly reduced expression [11]. In ischemic heart failure, however, the role of apelin—APJ is less clear. Both upregulation and downregulation of the apelin—APJ receptor system have been reported [27,28]. The cardiac apelin system is regulated by the angiotensin II–angiotensin type 1 receptor system directly. The cardiovascular effects of apelin are not mediated by the angiotensin II type 1 receptor [42], however, the inhibition of the renin–angiotensin system have beneficial effects, at least in part, through restoration of the cardiac apelin system in the treatment of HF [43].

To estimate the influence of apelin on infarct size, some animal studies based on ischemia/reperfusion model have been conducted. It was shown that apelin enhanced by ischemia/reperfusion injury, improves cardiac dysfunction by suppressing myocardial apoptosis and resisting oxidation effects [44]. In another ischemia/reperfusion rat model, apelin-13 reduced infarct size and limited the posts ischemic myocardial contracture [45].

4.2. Human studies

The findings from preclinical models could be translated into human studies. Apelin—APJ expression is altered in patients with chronic heart failure (CHF). Initial reports suggested that plasma apelin concentrations were mildly elevated in the early stages of heart failure, but fell with more advanced disease [18,19]. In patients with severe CHF, the improvement in New York Heart Association (NYHA) symptoms class and LVEF following cardiac resynchronisation therapy together with the increase of plasma apelin concentration were found [46]. Therefore, current data strongly suggest that apelin expression is at least maintained and possibly augmented in mild, compensated heart failure, but declines with advancing disease. Moreover, apelin plasma levels are reported to increase especially in the early stage of left ventricular dysfunction [19]. Upregulation of apelin mRNA was observed in myocardium from ischemic heart failure patients [18], and downregulation of apelin mRNA in myocardial injury [28]. Such equivocal findings might stem from the different time points post-infarction at which apelin expression was measured or might be the result of differences in heart failure severity leading to the concomitant activation of other interfering pathways. In order to further elucidate the role of apelin—APJ in ischemic heart failure, it is therefore important to know how the apelin receptor system in the heart responds to an ischemic insult independently of all other factors.

Interesting findings have been found by Földes et al. [18]. They compared circulating plasma apelin levels to the tissue apelin-like immunoreactivity expression in patients with heart failure and healthy men. Apelin was found to be present in normal human plasma. However, plasma levels of apelin were significantly decreased in patients with heart failure (III NYHA class) due to coronary heart
disease compared to normal subjects. On the other hand, left ventricular apelin mRNA levels were significantly increased in patients with heart failure due to coronary heart disease or idiopathic dilated cardiomyopathy. Although left ventricular apelin levels tended to be higher in patients with coronary heart disease and idiopathic dilated cardiomyopathy, these changes were not statistically significant. Apelin-like immunoreactivity expression was 200-fold higher in atrial tissue than ventricular tissue and correlated well with plasma apelin concentrations suggesting it may be the major source of circulating apelin. The changes in atrial and ventricular mRNA and peptide levels of apelin observed in the present study resembled those of ANP [47]. Thus, the induction of apelin gene expression in the failing ventricles, similar to ANP, constitutes an adaptive mechanism triggered by increased cardiac overload.

However, recent data have produced conflicting findings. Chong et al. reported that plasma apelin concentrations are decreased in patients with severe CHF. About 50% of the investigated patients had CHF due to ischemic heart disease and the majority of them displayed severe heart failure (73% were at NYHA class III or IV, and the mean ejection fraction was 15%) [48]. Goetze et al. have demonstrated that plasma apelin concentrations were decreased in patients with decreased LVEF (median 20%) due to CHF of mixed etiology, but even more in patients with parenchymal lung disease and idiopathic pulmonary hypertension and preserved left ventricle ejection fraction (median LVEF 65% and 60%, respectively) [49]. In patients with idiopathic dilated cardiomyopathy (LVEF <45%) plasma apelin levels were similar as compared to healthy control subjects [50]. The discrepancy of these results may be largely caused by the differences in study populations.

5. Apelin as a therapeutic target in heart failure?

Japp and co-workers were the first to demonstrate an influence of acute administration of apelin-36 infusion on human cardiovascular system in vivo [51]. Apelin was injected into peripheral artery as well as intracoronary bolus was given in order to measure coronary blood flow and LV contractility and pressures. Intravenous infusion of apelin was given for the systemic hemodynamic study. They were able to demonstrate peripheral and coronary vasodilation, improvement of myocardial contractility, reduction of LV pressures and rise in cardiac output. Hemodynamic results during apelin infusion were similar in healthy volunteers as well as in patients with coronary artery disease and heart failure. Thus apelin may become a very interesting therapeutic agent in patients with severe heart failure. From the other experiments it is known that, in contrast to another inotropic agents, long time apelin administration does not induce LV hypertrophy, moreover, by simultaneous reduction of loading condition and cardiac work oxygen demand is diminished [51].

Summarizing, there is still a way to establish apelin as a therapeutic agent for heart failure, especially chronic heart failure. The long term effect of apelin and the direct effect of apelin in stimulating the heart cells are still not well studied.

6. Conclusions

In summary, available data from animal and human studies suggest that apelin–APJ system is:

1. upregulated in response to hypoxia/ischemia
2. maintained or augmented in chronic pressure overload and the early stages of heart failure
3. essentially downregulated in severe heart failure.

The studies confirm the validity of apelin as a new adipokine of cardiovascular importance. Still available data do not give responses to all questions. Existing studies provide sparse data. Experimental and clinical investigations performed both in vivo and in vitro on various populations do not clarify the real significance of apelin. What is the exact diagnostic and prognostic role of apelin in AMI patients? Is apelin a goal for treatment in AMI or a new substance for the treatment in patients with heart failure especially of ischemic origin? Thus, there is a need to perform a prospective study with a homogeneous population to answer the above doubts.

References


