Apelin and vascular dysfunction in type 2 diabetes

Olaf Grisk*

Department of Physiology, University of Greifswald, Greifswalder Str. 11c, D17495 Karlsburg, Germany

Received 21 March 2007; accepted 30 March 2007
Available online 4 April 2007


The apelin receptor APJ belongs to the family of seven-transmembrane domain receptors and is coupled to inhibitory G-proteins [1,2]. Apelin is synthesized as a 77 amino acid pre-pro-peptide that can be cleaved into fragments of different sizes that activate APJ [1,2]. Apelin peptides have been shown to affect many biological functions in mammals including the neuroendocrine, cardiovascular, and immune systems [1]. It can act via autocrine, paracrine, endocrine, and exocrine signalling [1].

In the cardiovascular system apelin has been shown to increase cardiac contractility when administered in pharmacological doses [3]. The implications of this effect have been discussed recently in this journal [4]. Exogenous apelin lowers arterial pressure in mice and rats [5,6]. This effect is largely due to vasodilation as a consequence of apelin-induced activation of the endothelial nitric oxide synthase (eNOS) [5]. However, in conscious sheep low doses of apelin induced no significant alterations in arterial pressure [7]. At a higher dose a clear biphasic arterial pressure response was observed consisting of initial hypotension followed by hypertension [7]. This was accompanied by reciprocal heart rate changes that were most likely baroreflex mediated [7]. These data suggest that the vascular actions of apelin may be complex and involve effects in addition to eNOS activation depending on the apelin dose, species, and other experimental factors. Data on apelin-induced contractions in isolated human saphenous vein preparations [8] and on apelin-induced stimulation of myosin light chain phosphorylation in rat and mouse vascular smooth muscle [9] support this notion.

Obesity (in particular abdominal obesity), hyperinsulinemia, dyslipidemia and overt type 2 diabetes are well known to contribute to cardiovascular disease. There is increasing evidence that an excess of pro-inflammatory mediators released from adipocytes and from inflammatory cells residing within the adipose tissue elicits systemic inflammation and thereby contributes to the development of cardiovascular disease in obese individuals [10]. Among these pro-inflammatory mediators are several interleukins, tumor necrosis factor-α (TNF-α), and interferon-γ [10]. Adipocytes have recently been demonstrated to synthesize apelin [11], and its content was elevated in adipocytes from different mouse models of hyperinsulinemia-associated obesity [11]. Furthermore, apelin plasma concentrations were elevated in obese compared to lean humans as well as in obese, hyperinsulinemic mice compared to lean mice [11]. A positive correlation between plasma insulin concentrations and adipocyte apelin mRNA expression has been shown in experiments with db/db mice (homozygotes for a leptin receptor defect mutation that causes obesity, hyperinsulinemia, and type 2 diabetes), heterozygous (db/+)) and wild-type (+/+)) mice [11]. It has been further demonstrated that adipocyte apelin expression is stimulated by insulin and TNF-α [11,12]. Thus, apelin has been identified as another adipocyte-derived mediator or adipokine that is up-regulated under conditions of hyperinsulinemia and obesity.

In the present issue of Cardiovascular Research work is presented that shows differential effects of apelin on vascular function in type 2 diabetic db/db mice vs. heterozygous controls [13]. The results point to a potential role of altered apelin/APJ function in vascular pathophysiology associated with the metabolic syndrome and type 2 diabetes. Data obtained in myograph experiments show that apelin reduced the enhanced vasoconstrictor response of db/db mouse aortic rings to angiotensin II most likely due to the activation of NO synthesis. Furthermore, apelin improved the impaired...
endothelium-dependent relaxation in \(db/db\) mouse aortic rings but did not affect the endothelium-dependent relaxation in aortic rings from \(db/+\) controls. In whole aortic tissue from \(db/db\) mice the authors found less mRNA and less protein expression of the apelin receptor APJ than in heterozygote controls. It remains to be determined whether APJ expression is reduced in the endothelium, vascular smooth muscle cells, or both cell types in \(db/db\) mouse arteries. This could help to explain why apelin improved endothelium-dependent relaxation in \(db/db\) mice but was without significant effect in \(db/+\) controls despite lower aortic APJ expression in the former. Consistent with the differential effects of apelin on endothelium-dependent relaxation in \(db/db\) vs. \(db/+\) mice, apelin treatment increased the phosphorylation of protein kinase B (Akt) and eNOS in aortic rings from \(db/db\) but not from \(db/+\) mice. In contrast, the degree of Akt and eNOS phosphorylation was less in aortas from \(db/db\) than from \(db/+\) mice under basal conditions [13].

Currently, the relationship between increased apelin release from adipose tissue [11], vascular dysfunction and enhanced vascular responsiveness to apelin [13] in \(db/db\) mice is not clear. Rapid desensitization of apelin-dependent Akt phosphorylation has been demonstrated in vitro [2]. Whether in vivo desensitization of APJ in the presence of chronically high plasma apelin levels and in vitro desensitization of APJ in aortic tissue can explain the findings by Zhong et al. [13] at least in part remains speculative. In addition, apelin expression could have been less in \(db/db\) than in \(db/+\) aortic tissue. Lower availability of autocrine- or paracrine-acting vascular apelin in \(db/db\) than in \(db/+\) mice could provide an additional or alternative explanation for the clear effects of apelin treatment on \(db/db\) vessels that were not observed in \(db/+\) vessels [13]. Together, these in vitro findings could be indicative for a dysfunction of the vascular apelin/APJ system in \(db/db\) mice in vivo. In this regard it should be mentioned that lower aortic apelin and APJ expression has been found recently in spontaneously hypertensive rats (SHR) vs. normotensive rats and exercise-trained SHR, respectively [14]. SHR are viewed by many authors not only as model organisms for genetically determined hypertension but also for the metabolic syndrome.

In the future, extension of the work on apelin and APJ from large conduit vessels to small arteries and studies on the regulation of vascular apelin and APJ as well as the application of apelin-specific antagonists [6] will provide further information about the physiological role of apelin in vascular function. Based on this information, we will eventually be able to decide whether apelin is indeed a “good peptide” in the vasculature that exerts vascular protection in type 2 diabetes as suggested by Zhong et al. [13].

References