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Atrial natriuretic peptide influence on nitric oxide system in kidney and heart

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Abstract

Atrial natriuretic peptide (ANP) and nitric oxide (NO) induce diuresis, natriuresis and diminish vascular tone. Our previous studies showed NO system is involved in ANP hypotensive effect. The aim was to investigate ANP effects on renal and cardiac NO-synthase (NOS) activity. Rats were divided into two groups: group I, infused with saline (1 h, 0.05 ml/min); group II, received ANP bolus (5 μg/kg) + ANP infusion (1 h, 0.2 μg/kg.min). NADPH-diaphorase activity (NADPH-d) was determined in kidney and heart. NOS catalytic activity was determined in renal medulla and cortex and cardiac atria and ventricle by measuring the conversion of L-[U^{14}C]-arginine to L-[U^{14}C]-citrulline. In group I, NOS activity was determined in basal conditions and plus 1 μM ANP and in group II, NOS activity was determined in basal conditions. NADPH-d was higher in group II than in group I in glomeruli, proximal tubule, cortical and medullar collecting duct, right atria and left ventricle. NOS activity was increased by in vitro ANP addition and, in vivo, ANP infusion in all the studied tissues. ANP treatment increases renal and cardiac NO synthesis. This effect would be independent on the hemodynamic changes induced by ANP. The activation of NO pathway would be one of the mechanisms involved in diuretic, natriuretic and hypotensive effects of ANP.

Keywords: Nitric oxide; Nitric oxide synthase; Atria; Ventricle; Renal medulla; Renal cortex

1. Introduction

The cardiovascular and renal actions of nitric oxide (NO) and atrial natriuretic peptide (ANP) are fundamental to the regulation of blood pressure [1,2]. NO is released from vascular endothelial cells in response to chemical mediators and shear stress, whereas ANP is a hormone released from the cardiac atria in response to hypervolemic states [3,4]. Both mediators possess multifaceted actions that coordinate to maintain cardiovascular and renal homeostasis, including reducing vascular tone and promoting natriuresis and diuresis. Both ANP and NO induce an increase in intracellular cGMP levels, but they do through different pathways. The cellular effects of ANP are mainly mediated via the guanylate cyclase-coupled natriuretic receptors, NPR-A and NPR-B [5,6]. These receptors are expressed on the surface of different types of cells, including endothelial cells, both arterial and venous smooth muscle, different cells of the nephron segments, ventricle and atrial myocytes, etc. [7–11]. On the other hand, NO is produced by NO synthase (NOS), which three isoforms (eNOS, nNOS and iNOS) are expressed in many tissues, including endothelium, vascular smooth muscle, specific segments of the nephron and the heart [12–14]. It is widely known that NO binds to the heme moiety of soluble guanylyl cyclase, leading to an increase in cGMP levels [15]. This increase in cGMP production, like the cGMP produced by ANP through particulate guanylate cyclase, leads to a decrease in intracellular Ca^{2+} levels through a multiple of proposed cascade events [1].

Several studies support the hypothesis that NO may be involve in the regulation of ANP release in heart but the results are controversial. NO release may tonically inhibit the secretion of ANP from cardiac myocytes [16]. In contrast, both L-arginine as well as L-NAME had no effects on basal ANP secretion in the perfused rat heart [17]. Other

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authors suggest that NO appears to regulate baseline ventricular relaxation in conjunction with ANP [18].

In addition, we provided evidence that ANP induces a hypotensive effect by enhancement of NOS activity in the vascular endothelium and NO production through the L-arginine–NO pathway, via the guanylate cyclase-coupled natriuretic receptors NPR-A and/or NPR-B [19].

Given that growing number of examples of the interplay of the ANP and NO, it is possible to postulate an interaction between both systems in the kidney and in the heart. In the present study, we evaluated the effects of ANP on NOS activity in kidney and in the heart.

2. Materials and methods

2.1. Animals

Male Wistar rats weighting 250–300 g from the breeding laboratories of the Facultad de Farmacia y Bioquímica (Universidad de Buenos Aires, Argentina) were used for each experimental group throughout all experiments. Rats were housed in a humidity and temperature-controlled environment with an automatic light/dark cycle of 12:12 h. Rats were fed with standard rat chow from Nutrimentos Purina (Buenos Aires, Argentina) and tap water ad libitum up to the day of the experiments.

2.2. Experimental design

Animals were used in compliance with the research animal use guidelines of the American Heart Association.

Rats were anaesthetized with urethane (1 g/kg body-weight, i.p.). The jugular vein was cannulated with a polyethylene catheter for saline infusion and ANP administration.

2.3. Protocol

After surgery, an infusion of isotonic sodium chloride at a rate of 0.05 ml/min was started and maintained for 40 min, to allow stabilization. At the end of this period, one group of animals received an isotonic saline infusion at a rate of 0.05 ml/min during 1 h and other group was injected with a bolus of ANP (5 μg kg^{-1}) and then received an ANP infusion (0.2 μg kg^{-1} min^{-1}) over 1 h.

At the end of the experimental period, the animals were sacrificed and kidneys and heart were removed in order to determine NADPH diaphorase (NADPH-d) activity and NOS activity.

2.4. Determination of NADPH diaphorase activity

Different tissues were fixed with 4% paraformaldehyde in 0.1 mol/l phosphate buffer pH 7.4, according to Rothe et al. [20]. The tissues were cryoprotected with sucrose and frozen, 15-μm sections were cut on a criostate and mounted on gelatin-coated glass slides. The sections were processed using the NADPH-d histochemical method. This technique is used as an histochemical marker of isozyme-independent NOS, since it has been demonstrated that NADPH-d activity is inhibited by preincubation with DPI, a potent inhibitor of NOS [21–23]. Sections were then mounted in PBS/glycerol (1:3). Observation, optical density (OD) measurement and photography were carried out on a Zeiss Axiophot microscope. The time and temperature of incubation with the reaction mixture were carefully controlled and the samples were randomly processed.

2.5. Computed image analysis

The NADPH-d-stained cells from the different groups were measured by using a computerized image analyzer (Kontron-ZEISS VIDAS). The mean of each OD value resulted from the measurement of OD in different tissue areas of the same section and different sections of the same organ. Each set of OD measurements (control and experimental groups) was performed blindly and under similar conditions of light, gain, offset and magnification.

2.6. Determination of NOS activity

NOS activity was measured in the renal medulla and cortex and in the left ventricle and right atria of the control and the ANP-infused animals, using [U-^{14}C] arginine as substrate as previously described [24,25]. Tissue slices (2–3 mm thick) were incubated 30 min at 37 °C in Krebs solution with 0.5 μCi/ml [^{14}C] L-arginine. The reaction was stopped by adding 500 μL stop buffer (0.5 mmol/l EGTA, 0.5 mmol/l EDTA, 20 mmol/l HEPES, pH 5.5). Tissues were homogenized in the stop solution. The homogenates were centrifuged at 12,000 × *g* for 20 min. The supernatants were then applied to a 1 ml Dowex AG 50W-X8 column (Na^+ form, Bio-Rad), hydrated with the stop buffer and eluted with 2 ml

Table 1
Effects of ANP on NADPH-d activity in kidney and heart

	OD	
	Control	ANP
Nephron		
Glomeruli	0.213 ± 0.002	0.258 ± 0.001*
Proximal tubule	0.163 ± 0.003	0.181 ± 0.003*
Cortical collecting duct	0.172 ± 0.003	0.198 ± 0.002*
Inner medulla collecting duct	0.243 ± 0.005	0.292 ± 0.001*
Heart		
Right atria	0.161 ± 0.001	0.209 ± 0.003*
Left ventricle	0.166 ± 0.002	0.217 ± 0.004*

Control ($n = 14$): tissues from animals that received saline infusion; ANP ($n = 12$): tissues from animals that received a bolus and an infusion of ANP. OD, optical density. Values represent the mean ± S.E.M. Data were analyzed using Student's *t*-test.

*$p < 0.001$ vs. control.

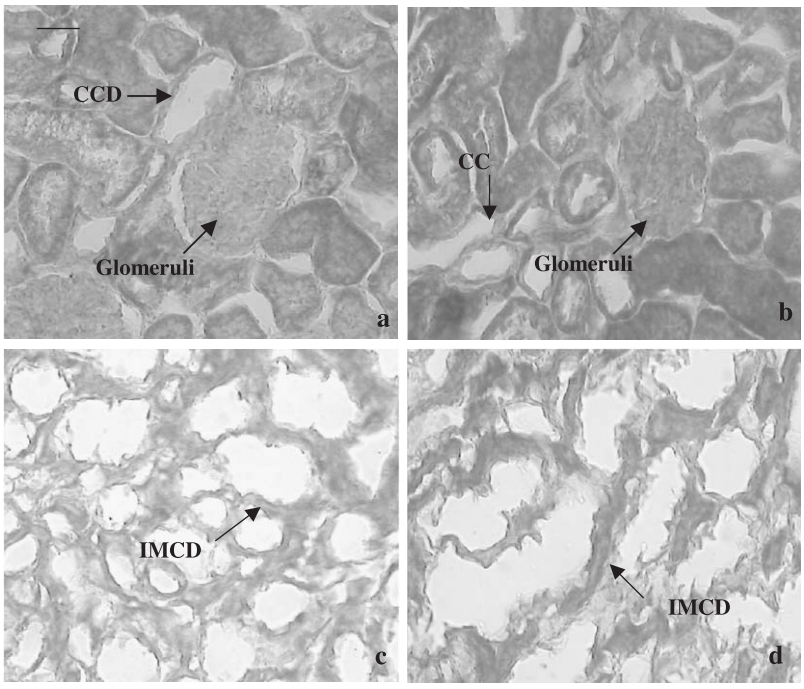

Fig. 1. Photomicrographs of the kidney NADPH-d (+) from control cortex (a), ANP cortex (b), control medulla (c) and ANP medulla (d). Note the intensity of renal medulla and cortex from the ANP-treated animals compared with controls. CCD, cortical collecting duct; IMCD, inner medulla collecting duct. All images at the same magnification. Scale bar = 30 μm.

distilled water. The amount of [^{14}C] L-citrulline was determined with a liquid scintillation counter (Wallac 1414 WinSpectral). Specific NOS activity was assessed in the presence of 10^{-4} M L-*N*-nitro-arginine methyl ester (L-NAME) (Sigma, St. Louis, MO, USA). Nitric oxide production (measured as pmol of [^{14}C] citrulline) in each tube was normalized to the weight of the tissue slices incubated with the substrate during equal (30 min) periods of time and

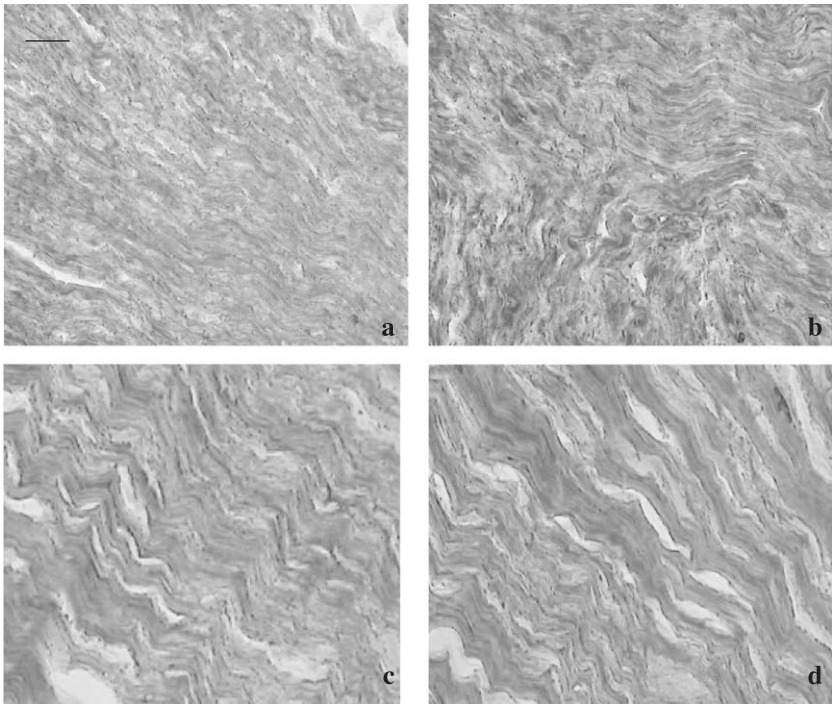

Fig. 2. Photomicrographs of the heart NADPH-d (+) from control atria (a), ANP atria (b), control ventricle (c) and ANP ventricle (d). Note the intensity of cardiac atria and ventricle from the ANP-treated animals compared with controls. All images at the same magnification. Scale bar = 30 μm.

thus expressed in pmol/g wet weight. When used, L-NAME was included from the beginning of the incubation time and ANP was added at the final concentrations indicated for the last 15 min. Control tissues were incubated in the presence or absence of ANP.

3. Statistical analysis

All values are expressed as means ± S.E.M. The program Prism (Graph Pad Software, San Diego, CA, USA) was used for statistical analysis. Data were analyzed using Student's *t*-test and one-way analysis of variance (ANOVA) followed by a Bonferroni multiple comparisons post hoc test. A p value of >0.01 was considered significant difference.

4. Results

Table 1 shows the activity of the NOS, evaluated by the NADPH-d activity, in the different segments of the nephron and cardiac atria and ventricle in rats that received ANP infusion and in control animals. Renal staining was more intense in glomeruli, proximal tubule, cortical and inner medulla collecting duct of the ANP-treated compared with control rats (Fig. 1). Animals that received ANP infusion showed a higher activity of NADPH-d in cardiac atria and ventricle than control ones (Fig. 2).

Table 2 shows NOS activity determined with [^{14}C] L-arginine in vitro method in kidney and heart of control and ANP-treated animals. Renal and cardiac tissues obtained from the animals that were infused with ANP showed an increased activity of NOS compared with control ones. When tissues of control animals were incubated in vitro with ANP, an increase in NOS activity was also observed in renal medulla and cortex as well as in cardiac atria and ventricle (Table 2). Enhanced NOS activity induced by ANP was blunted when L-NAME was added previously (Table 2).

5. Discussion

Atrial natriuretic peptide exerts its diuretic and natriuretic effects through its receptors in the different segments of the nephron [11].

It is known that ANP increases glomerular filtration rate through its vasodilator effect on afferent artery and enhancing the filtration surface by relaxing mesangial cells [26,27]. In addition, Ytoh et al. [28] demonstrated that NPR-C receptor expression was most abundant in glomeruli. It is also known that NO produces relaxation in glomerular arteries, including afferent arteriole, and in mesangial cells resulting in an increase in glomerular filtration rate [29]. The augmented NOS activity in the glomeruli in response to ANP infusion observed in the present study, would indicate that NO pathway activation may be one of the mechanisms involved in the increase of filtration rate induced by the peptide and the receptor that participate could be NPR-C.

In the proximal tubule, studies addressing the ANP effects and its receptors have providing conflicting results. McLay et al. [30] showed that, in culture of tubular cells, ANP inhibits, via cGMP, iNOS activity involving NPR-C. In contrast, other authors showed that primary cultures of human proximal tubular cells can be stimulated to produce NO by ANP [31]. In addition, it was demonstrated that natriuretic effects of ANP are diminished by dopamine D1-like receptor antagonists, suggesting that ANP actions in proximal tubule are mediated by dopamine [32,33]. In previous studies, we demonstrated that renal DA could stimulate the NO pathway and this mechanism would mediate the renal effects induced in volume expansion condition in which high levels of ANP are reported [34]. This fact indicates that the enhanced activity of NOS

Table 2
NOS activity in kidney and heart in control animals, in presence or absence of ANP, and in ANP-infused animals

	Control	NOS activity (pmol/g tissue)				
		C + L-NAME	C + ANP	C + ANP + L-NAME	ANP infusion	ANP infusion + L-NAME
Kidney						
Medulla	418.06 ± 6.13	386.08 ± 7.43	531.98 ± 13.54*	389.14 ± 8.47†	521.01 ± 9.01*	376.52 ± 9.12‡
Cortex	318.39 ± 9.78	299.79 ± 8.84	375.77 ± 12.85*	305.14 ± 7.13†	412.11 ± 5.47*	301.30 ± 7.14‡
Heart						
Right atrium	203.12 ± 5.92	192.19 ± 6.02	259.52 ± 6.19*	197.60 ± 7.15†	267.52 ± 5.13*	195.19 ± 7.19‡
Left ventricle	149.53 ± 8.32	139.32 ± 9.14	188.48 ± 7.45*	132.08 ± 7.08†	177.42 ± 9.37*	139.32 ± 9.14‡

Control (n = 14): basal NOS activity of the tissues of the control animals; C + L-NAME (n = 10): in vitro blockade of basal NOS activity of the tissues of the control animals; C + ANP (n = 10): NOS activity of the tissues of the control animals after ANP addition in vitro; C + ANP + L-NAME (n = 9): NOS activity of the tissues of the control animals after L-NAME and ANP addition in vitro; ANP infusion (n = 12): basal NOS activity of the tissues of the animals that received ANP bolus and infusion in vivo; ANP infusion + L-NAME (n = 10): basal NOS activity of the tissues of the animals that received ANP bolus and infusion in vivo with in vitro blockade. Values represent the mean ± S.E.M. Data were analyzed using one-way analysis of variance (ANOVA) followed by a Bonferroni multiple comparisons post hoc test.

* p < 0.01 vs. control.

† p < 0.001 vs. C + ANP.

‡ p < 0.001 vs. ANP infusion + L-NAME.

observed in proximal tubules in ANP treated rats may be probably the result of an activation of dopamine system in proximal tubular cell.

The mechanisms involved in cortical collecting duct effects of ANP are not well clarified. It was reported that NPR-A receptor was identified inmunohistochemically in rat, in principal and intercalated cells of cortical collecting duct [35,36]. Nonoguchi et al. [37] demonstrated that ANP inhibits NaCl and fluid reabsorption both under basal and after stimulation with vasopressin in isolated cortical collecting duct. In the present study, we showed that ANP increased NOS activity in this section of the collecting duct, suggesting that NO system could participate, at least in part, in the diuretic and natriuretic ANP actions at this nephron segment.

Inner medulla collecting duct is the principal site of action for ANP, at least under physiological conditions. Apart from glomeruli, this segment contains the highest amounts of ANP receptors [38]. Several lines of evidence indicate that the effect of ANP in inner medulla collecting duct is mediated by NPR-A receptors and cGMP [39–41]. In addition, data indicate that ANP participates in the regulation of sodium reabsorption by the inhibition of amilorida-sensitive Na^+ uptake and Na^+K^+ATPase activity and the decreasing of Camp [42–44]. On the other hand, these mechanisms are also involved in NO natriuretic response because both ANP and NO increase cGMP [45–48]. However, our results showed that ANP increased NOS activity in the inner medulla collecting duct, indicating that one of the mechanisms that participates in ANP natriuretic actions would be the activation of NO system, probably involving NPR-A or NPR-B.

The increased NOS activity observed in nephron segments is in agreement with our previous findings that showed an augmented NO_x-derived end products (nitrites and nitrates) excretion induced by ANP infusion in rats [19].

Meanwhile, shear stress due to the increase of renal plasma flow induced by ANP could stimulate NO production, we observed an enhanced activity of NOS in response to ANP addition in vitro to renal medulla and cortex. This fact indicates that the peptide effects on NO pathway are not only due to the hemodynamic changes induced when the peptide is administered in vivo.

With respect to the heart, three types of ANP receptors have been demonstrated in cardiac atria and ventricle [8,10,49]. Nachshon et al. [50] defined an autoregulatory mechanism of ANP secretion by atrial myocites in a autocrine/paracrine manner, involving NPR-C. Taking in account these findings and our in vivo and in vitro results that showed an activation of atrial NOS in response to ANP, we suggest that NO would participate in the autoregulatory mechanism of synthesis and/or secretion of ANP.

Previous reports showed that ANP and NO pathway participate in the regulation of cardiac ventricle function. In vitro studies demonstrate that low and moderate concentrations of natriuretic peptides have a positive inotropic effect [51]. On the other hand, Gyurko et al. [18] provided evidence that in intact animals and in the isolated Langendorff heart preparation, the eNOS isoform attenuates systolic contractility response. Meanwhile, in vivo and in vitro data indicate that, under basal conditions, cardiac function is normal in eNOS knockout model suggesting NO would only play a minor role in basal cardiac function, but in beta adrenergic stimulation condition eNOS would mediate the negative inotropic effect [52]. Taking into account these findings, our results suggest that NO would not be implicated in ANP-mediated inotropic effects.

Accordingly our previous findings in aorta artery and arterioles, the present results support the hypothesis of a close relationship between NO system and ANP in the regulation of cardiovascular and renal functions.

6. Perspectives

The atrial natriuretic peptide and NO are two systems that regulate cardiovascular and renal function. It is reasonable to project that a growing number of examples of the interplay of the atrial natriuretic peptide and nitric oxide in human health and disease will be established and that these molecules will be increasingly exploited in the diagnosis, risk assessment, and therapy of cardiovascular and renal diseases.

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