Interactions between bradykinin and ANP in rat kidney *in vitro*: Inhibition of natriuresis and modulation of medullary cyclic GMP

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In anesthetized rats, the renal excretory actions of atrial natriuretic peptide (ANP) are inhibited by intravenous or intraperitoneal injections of bradykinin. To elucidate the mechanisms underlying this inhibition, we evaluated bradykinin effects on: ***i****- ANP-induced natriuresis and diuresis in isolated perfused rat kidneys, and* ***ii****- ANP-induced cGMP production in rat renal medulla* ***in vitro****. In perfused kidneys, 1 μg bradykinin completely inhibited the diuretic and natriuretic responses elicited by 0.5 μg ANP, without changes in perfusion pressure. The inhibitory effects of bradykinin were abolished by HOE-140, a kinin-B_2 receptor antagonist. Bradykinin alone had no effect on urinary excretion or perfusion pressure. Incubation with ANP (0.1 nM to 1 μM) increased renal medullary cGMP content up to 30-fold, in a concentration-dependent fashion. Medullary cGMP was moderately increased by the nitric oxide donor, sodium nitroprusside (1 μM), but it was unchanged by bradykinin (0.1 nM - 0.1 μM). Despite this, ANP-induced cGMP production was significantly enhanced by co-incubation with low concentrations of bradykinin (up to 0.1 nM). In contrast, ANP-induced cGMP accumulation was unchanged by concentrations of 1 nM bradykinin or higher. In the presence of 100 nM HOE-140, bradykinin (0.1 - 1 nM) did not affect ANP-induced cGMP production. These results demonstrate that bradykinin counteracts ANP-stimulated sodium and water excretion, by acting directly on the kidney. The interaction between both peptides is complex; our data suggest that renal medullary ANP receptors are subjected to an on/off modulation by fluctuating bradykinin concentrations.*

Key terms: *atrial natriuretic peptide, atriopeptin II, bradykinin, cGMP, HOE-140, kidney, kinins, natriuresis, pepsanurin*

INTRODUCTION

Atrial natriuretic peptide (ANP) exerts potent vascular and renal tubular actions that allow this hormone to partake in short and long term regulation of sodium and extracellular fluid homeostasis (reviewed in ref 5). In anesthetized rats, the excretory action of ANP is antagonized by a pepsin hydrolysate from fresh human or rat plasma, named pepsanurin (PU) (10), when injected either in the peritoneal cavity (3)

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or the duodenal lumen (11). Furthermore, pepsanurin blocks the excretory effect of ANP in isolated perfused rat kidneys (3), suggesting an intrarenal mechanism of action opposed to ANP. The anti-ANP effects of pepsanurin occur in the absence of any detectable change in arterial or perfusion pressure.

More recently, we have demonstrated that kinins present in pepsanurin are the chemical agents responsible for inhibition of ANP (2, 4). This assertion is based on two findings. First, in anesthetized rats, sodium, potassium, water and guanosine 3':5'-cyclic monophosphate (cGMP) excretion induced by a bolus of 0.5 μg ANP are importantly blocked by the intravenous or intraperitoneal injection of bradykinin. Second, the anti-ANP effects of pepsanurin are completely prevented by the kinin receptor antagonist HOE-140. In addition, the intravenous, intraperitoneal or intraduodenal injection of pro-kinin peptides containing the bradykinin sequence also elicits the anti-ANP effect (12, 13). Moreover, the excretory response to ANP is greatly reduced in rats treated with a kininase II inhibitor, and this effect depended on endogenous kinins since it is abolished by HOE-140 (2).

The above results suggest that kinins can act intrarenally to block ANP, perhaps by interfering with ANP transduction mechanism. Biological effects of ANP are mediated by activation of the particulate form of guanylate cyclase, known as GC-A-ANP or B_A-ANP receptor, and subsequent intracellular cGMP production (5, 17, 19). Nevertheless, to date, there is no demonstration that kinins may inhibit ANP-induced urinary excretion in isolated kidneys, and there are yet no studies focused on a possible modulatory effect of kinins on the ANP signaling pathway.

The purpose of this study was two folds: firstly, we used the isolated perfused rat kidney technique to assess the hypothesis that bradykinin inhibits ANP excretory effects by acting directly on the kidney; secondly, we studied whether bradykinin influenced renal ANP transduction mechanism by measuring the production of cGMP in response to ANP in the isolated rat renal medulla *in vitro*. We choose to study the renal medulla because ANP excretory action depends mostly on activation of receptors located in the inner medullary collecting duct (5, 34). In addition, this portion of the kidney contains only GC-A-ANP receptors (14, 28), as opposed to glomeruli, which present a large population of C-ANP or clearance ANP receptors (19).

METHODS

All studies were conducted following institutional and international policies in compliance with the Guiding Principles in the Care and Use of Laboratory Animals endorsed by the American Physiological Society.

Materials

$ANP_{103-125}$ (atriopeptin II, rat form), bovine serum albumin (BSA; fraction V), bovine serum albumin (BSA), bradykinin triacetate (BK) and 3'-5'cyclic GMP (cGMP), 2'-0-succinyl-cGMP-tyrosyl-methyl-ester were from Sigma Chemical (St Louis, MO, USA). All other chemicals were from E Merck (Darmstadt, Germany). Kinin B_2-receptor antagonist HOE-140 (D-Arg-[Hyp^3, Thi^5, D-Tic^7, Oic^8]bradykinin) was generously provided by Hoescht (Mainz, Germany).

Isolated perfused rat kidney.

Adult, male Sprague-Dawley rats (250-270 g bw) were anesthetized with sodium pentobarbital (40 mg, ip) and injected with 200 mU of heparin through the femoral vein. The right kidney was prepared for perfusion with a technique previously described in detail (24). Briefly, a PE-10 catheter was inserted in the right ureter and a metal cannula was inserted into the right renal artery through the superior mesenteric artery. Renal perfusion was started immediately and the kidney was removed and placed in a plexiglass chamber kept at 37°C. The perfusion medium was a modified

bicarbonate Krebs-Henseleit solution supplemented with 7% dialyzed BSA, 2 mM pyruvate, 5.6 mM glucose, and 6 mM urea. The solution was constantly equilibrated and buffered at pH 7.4 with a mixture of 95% O_2 and 5% CO_2. The perfusion medium was recirculated continuously at constant flow with a peristaltic pump. Perfusion pressure was measured near the tip of the arterial cannula and recorded in a Grass polygraph. Flow was adjusted at the beginning of the experiment to give a pressure of 90-100 mm Hg. In all experiments, perfusion flow was between 27 and 32 mL/min. The kidney was washed for 20 min with *ca.* 100 mL of medium; then the experiment was started by connecting a second reservoir with 60 mL of fresh perfusion medium. The test substances were added directly to the circulating medium at indicated times.

The experiment consisted of 1-h perfusion, divided in four periods of 15 min for urine collection. Urinary volume and sodium were determined by gravimetry and flame photometry, respectively. Four different experimental protocols were performed. The response to ANP was assessed in the first group by adding 0.5 µg ANP at the start of the third collection period (Control, n=9). This ANP dose equals the amount given iv to anesthetized rats in our previous studies (2-4, 11-13), and it was found to be effective to induce a diuretic-natriuretic response in the isolated kidney preparation (29). The estimated ANP concentration in the perfusion medium was *ca.* 3.5 nM. In the second group, 0.5 µg ANP was added at the start of period 3 as in the control, but this was preceded 3 min earlier by 1 µg bradykinin (BK, n=7). This bradykinin dose (approximate concentration of 13.3 nM) was chosen based on its effectiveness to inhibit ANP in anesthetized rats (4). The third group received 0.5 µg ANP and 1 µg bradykinin as before, with the difference that 2 µg of the specific B_2-bradykinin receptor antagonist HOE-140 (18) was added just before bradykinin (BK+HOE, n=6). HOE-140 was applied in excess of a 1:1 molar ratio to block bradykinin. The fourth experimental group received 1 µg bradykinin at the start of period 3, without ANP, to assess the effect of bradykinin alone on diuresis, natriuresis and perfusion pressure.

Determination of renal medullary cGMP.

Male rats (250-300 g bw) were decapitated and their kidneys quickly removed and handled on ice. Kidneys were cut in halves and their whole renal medullas were isolated with fine surgical scissors. Both renal medullas from every rat were used in each determination. The medullas were blotted, weighed, minced with scissors, and pre-incubated during 4 min at 37°C in 12x75 mm plastic tubes with 300 or 400 µl Hank's solution supplemented with 2.0 mg BSA, 5.5 mM glucose, 25 mM HEPES, pH 7.4. The volume was completed to 500 µl with Hank's solution containing ANP, bradykinin, HOE-140, or a combination of these agents to a desired final concentration, and incubated for additional 3 min. The incubation was stopped by the addition of 500 µl cold 15% trichloroacetic acid. The tube was transferred to ice and the tissue was quickly homogenized with an Ultraturrax. After centrifuging, the supernatant (*ca.* 1 ml) was kept on ice and extracted three times with 3 ml water-saturated ether (14, 22). The aqueous phase was lyophilized and stored at -20°C for cGMP determination.

A concentration-response curve for ANP was performed (range 0.2 nM to 1 µM ANP) in the absence or presence of 0.1 nM bradykinin. The concentrations of 20 nM and 100 nM ANP lay in the slope section of the curve, and were chosen as appropriate to study the effects of different bradykinin concentrations on ANP-induced cGMP production. In separate experiments, bradykinin (to a final concentration of 0.01 to 100 nM) was added 1 min before ANP, during the pre-incubation period. Bradykinin concentrations of 0.1 nM and 1 nM were found most effective to modulate the ANP-induced response. Therefore, in another experimental series, the tissue was pre-incubated for 1 min with 100 nM HOE-140 before adding 0.1 nM or 1 nM bradykinin, followed 1 min later by 100 nM ANP. Appropriate controls were done to assess the direct effect of bradykinin and HOE-140 on renal medullary cGMP production. In

addition, to assess the possible contribution of soluble guanylate cyclase (from vascular sources) (20), we measured cGMP content after incubating the renal medulla with 1 µM sodium nitroprusside, used as an exogenous nitric oxide donor.

The cGMP content accumulated in renal medulla homogenates was determined using a radioimmune assay (RIA) as described (2, 4). Briefly, lyophilized homogenates were resuspended in 600 µl RIA buffer (0.05 M sodium acetate, pH 6.2). Duplicate 100 µl samples were acetylated by adding 10 µl triethylamine: acetic anhydride (2:1) and incubated overnight at 5 °C in 500 µl RIA buffer containing anti-cGMP antibody (1:40,000) and 10,000 cpm ^{125}I-2'-0-succinyl-cGMP-tyrosyl-methyl-ester. Similar tubes containing 10 - 1,000 fmol acetylated cGMP were used for the standard curve. The cGMP-antibody complex was precipitated with 50% ammonium sulphate. Bound counts were detected in an LKB-Wallac gamma counter equipped with an automatic RIA program. Cyclic GMP production was expressed as fmol cGMP per min incubation (in the presence of ANP) per mg wet tissue.

Data are presented as means ± SEM's. Statistical analysis of differences was carried out by either paired Student's *t* tests to compare changes within each group, or by one-way ANOVA, followed by Newman-Keuls tests to compare differen-ces among groups.

RESULTS

Isolated perfused kidneys.

During baseline collection periods there was no difference among experimental groups in urinary flow, natriuresis or perfusion pressure (Fig 1). Addition of 0.5 µg ANP induced significant increases in urinary volume and sodium excretion in periods 3 and 4, without changes in perfusion pressure. However, when 1 µg bradykinin was added to the perfusion medium, ANP did not produce any increase in diuresis or natriuresis. In contrast, in the presence of bradykinin plus B_2-kinin receptor antagonist HOE-140, the response of the isolated kidney to ANP was similar to the control (Fig 1). A comparison of urinary

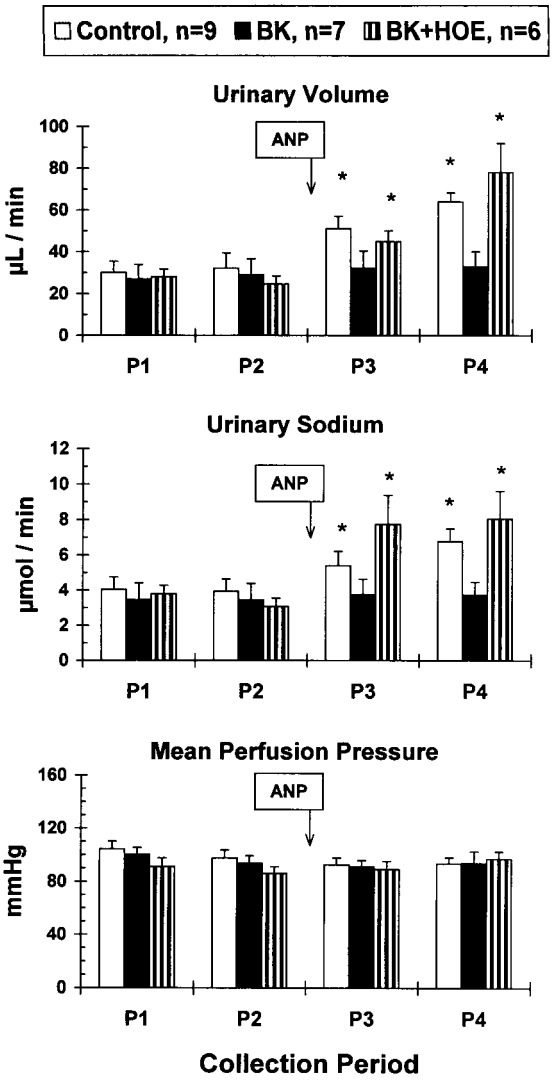

Fig 1. Values in urinary volume (top), urinary sodium (middle) and perfusion pressure (bottom) in three groups of isolated perfused rat kidneys studied during four periods of 15 min each. In all three groups, 0.5 µg ANP was added to the perfusion medium (60 mL) at the start of period 3. Three min before ANP, one group received 1 µg bradykinin (BK; black columns), and other group received 1 µg bradykinin plus 2 µg HOE-140 (BK+HOE; hatched columns). Means + SEM's. Asterisks, significant differences from period 2 ($p < 0.05$; paired Student's *t* tests).

excretion among groups revealed that –during period 4– diuresis and natriuresis were significantly lower in bradykinin-treated kidneys than in the other two groups ($p < 0.02$; ANOVA, Newman-Keuls test).

The dose of 1 µg bradykinin that was effective to block ANP renal actions, did not modify diuresis or natriuresis (Table I), nor affected perfusion pressure when given alone.

Table I

Effects of bradykinin on urinary excretion in isolated rat kidneys (n = 5).

Period	1	2	3	4
Urinary Volume (μL)	603 ± 140	606 ± 157	525 ± 113	504 ± 89
Urinary Sodium (μmol)	72.4 ± 4.2	70.0 ± 6.8	69.5 ± 8.6	69.1 ± 9.4

1 μg bradykinin added to perfusion medium (60 mL) at start of period 3.
No significant differences observed (paired Student's t tests).

Renal medullary cGMP production.

Unstimulated renal medulla contained 3-7 fmol cGMP/mg tissue. Incubation with ANP produced a dose-dependent increment in cGMP content that reached a plateau above 1 μM (Fig 2, upper panel). In the conditions described here, medullary cGMP production/ accumulation was not changed by incubation with 0.1 or 100 nM bradykinin, but it was moderately increased by 1 μM sodium nitroprusside (Fig 2, lower panel).

Surprisingly, co-incubation of renal medullas with low concentrations of bradykinin increased ANP-induced cGMP accumulation. The whole cGMP *vs* ANP concentration-response curve was significantly shifted to the left in the presence of 0.1 nM bradykinin (Fig 2). The influence of bradykinin concentrations on this enhancing effect was studied in more detail in medullas stimulated with 20 or 100 nM ANP (Fig 3). For both ANP concentrations tested, co-incubation with low concentrations of bradykinin (0.1 pM to 0.1 nM) enhanced cGMP production. However, when medullas were incubated with concentrations of 1 nM bradykinin or higher, ANP-stimulated cGMP production was unchanged, as compared with the control value without bradykinin (Fig 3).

Treatment with 100 nM HOE-140 produced significant increments in basal and ANP-stimulated cGMP (Fig 3, bottom). On the other hand, in the presence of HOE-140, neither 0.1 nM nor 1 nM bradykinin modified cGMP production stimulated by 100 nM ANP (Fig 3, bottom).

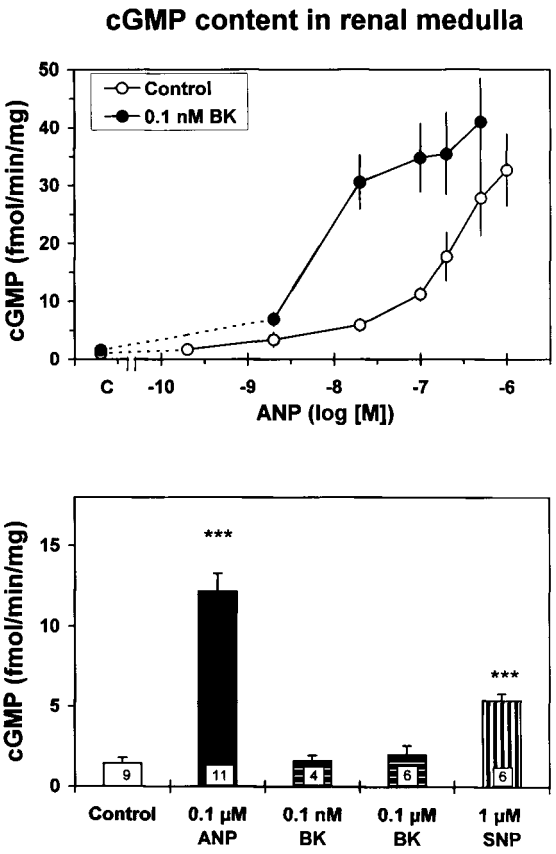

Fig 2. Top: Concentration-response relationship between ANP and cGMP production in rat renal medulla. Renal medullas were incubated 3 min with the given concentrations of ANP, at 37°C in Hank's solution, in absence (c, controls; open circles) or presence of 0.1 nM bradykinin (BK; filled circles). Mean ± SEM's of 5–7 experiments. **Bottom:** Cyclic GMP production in rat renal medullas incubated with Hank's solution alone (control), or supplemented with 0.1 μM ANP, 0.1 nM bradykinin (BK), 0.1 μM bradykinin, or 1 μM sodium nitroprusside (SNP) during 3 min. *** = $p < 0.001$ *vs* control; ANOVA, Newman-Keuls test.

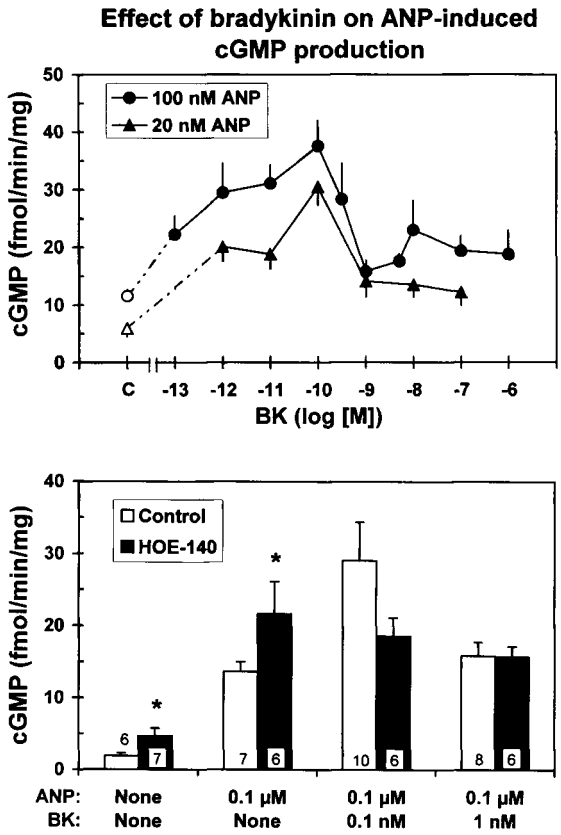

Fig 3. Top: Modulation of ANP-induced cGMP production by bradykinin. Rat renal medullas incubated with either ANP alone (open symbols) or ANP plus the concentrations of bradykinin filled symbols) shown in the abscissa. Low bradykinin concentrations elicited a parallel increase in cGMP production induced by either 20 or 100 nM ANP. In the range of 1-10 nM bradykinin, cGMP production was similar to control. Means ± SEM's of 5–8 determinations. **Bottom:** Effect of bradykinin antagonist HOE-140 on cGMP production. Bars, cGMP production in renal medullas incubated with ANP and/or bradykinin concentrations shown under the bars, in absence (Control; open bars) or presence of 100 nM HOE-140 (black bars). Means + SEM's (n at the bottom of bars). Asterisks, significant differences respect to control ($p < 0.05$; Student's t tests). Note that bradykinin in the presence of HOE-140 did not enhance, nor reduce ANP-induced cGMP production.

DISCUSSION

The present results clearly demonstrate that non-vasodilator, non-natriuretic doses of bradykinin exert a marked inhibition of ANP natriuretic and diuretic effects by acting directly on the isolated perfused rat kidney. This finding extends our previous reports showing that bradykinin inhibited ANP in anesthetized rats (2, 4). In addition, this result may explain our earlier report that pepsanurin inhibits the diuretic-saluretic effects of ANP in the isolated perfused rat kidney (3). As in the case of the anesthetized rat, the anti-ANP effects of bradykinin are not accompanied by changes in perfusion pressure, and are abolished by HOE-140, a specific antagonist of B_2-kinin receptors.

In vivo, ANP excretory effect was blocked by bradykinin injected at precisely small doses, either in the range of 100 -150 ng per rat, when given iv 3 min prior to 0.5 µg ANP (2), or between 0.5-2 µg per rat, when injected ip 40 min prior to ANP (4). In the conditions described here, 1 µg bradykinin was dissolved in 60 mL perfusion medium, giving an initial concentration of approx 13 nM. Time sampling of the perfusion medium confirmed that bradykinin concentration remained within this order of magnitude for the duration of the experiment, as measured by RIA (data not shown). Therefore, our first observation in isolated kidneys tends to confirm the speculation advanced previously, that to exert its anti-ANP action, bradykinin should reach the kidney at concentrations around the 1-10 nM range (2). At this moment, we don't know the concentration dependency, or the duration of the inhibitory effect caused by bradykinin on ANP stimulation of natriuresis and diuresis in isolated kidneys. From a physiological perspective, two interesting questions are to know whether intrarenal kinin concentration may reach the inhibitory level, and whether kinin concentrations fluctuate around this level, providing a mechanism to reversibly modulate the diuretic effect of ANP in different conditions. Kinin concentrations around 1-10 pM have been measured in rat kidney homogenates (7); however, the components of the renal kallikrein-kinin system are localized in the distal nephron, allowing for marked variations in kinin concentrations in distal and medullary segments (30). For instance, interstitial renal kinin levels decrease dramatically in rats submitted to a high sodium intake (26), while renal kinins increase in dogs and rats under a low sodium diet (26, 27). In this context, it has been postulated that an

enhanced activity of the kallikrein-kinin system counteracts the effects of the renin-angiotensin system, preventing an exacerbated sodium retention (27). However, the possibility that increased intrarenal kinins may contribute to sodium retention by inhibiting the excretory action of natriuretic peptides warrants further exploration. A possible role of endogenous kinins as inhibitors of ANP diuretic effect is supported by reports that humans treated with inhibitors of angiotensin converting enzyme (ACE), which is also the kininase II, present a blunted natriuretic effect to exogenous ANP (16, 32). Similarly, the natriuresis produced during inhibition of neutral endopeptidase, a maneuver that increases endogenous ANP levels, is not observed in subject treated with ACE inhibitors (21). Although these results had been largely ascribed to reduced angiotensin II levels, we demonstrated that, a similar inhibition of ANP induced natriuresis by ACE inhibitors is completely reversed by blockade of B_2-kinin receptors in the rat (2). Interestingly, a recent report shows that bradykinin antagonist HOE-140, restores sodium excretion in sodium-retaining cirrhotic rats (33).

To get insight into the mechanisms involved in the inhibitory effect of bradykinin, in the second part of this study we assessed whether bradykinin modifies the ANP-evoked cGMP production of the isolated rat renal medulla. Most of ANP natriuretic-diuretic effects depend on inhibition of sodium reabsorption in inner medulla (5, 34, 35). To this date, only GC-A type of ANP receptor has been reported in renal medullary tubules (14, 19). On the other hand, all known physiological effects of bradykinin are mediated by stimulation of B_2-kinin receptors, although B_1-bradykinin receptors may participate in some pathophysiological states (1). In the kidney, B_2-kinin receptors are localized in distal tubules, and cortical and medullary collector tubules (15, 31). There is functional evidence for action of both ANP and bradykinin on epithelial transport at the same collector tubule segments (35). In addition, both hormones are thought to favor natriuresis by increasing inner medullary blood flow and/or interstitial pressure (1, 5, 35). Thus, the simple experimental model here described provides a first approach to study a possible direct interaction between bradykinin and ANP, without influence from changes in blood flow or transepithelial forces that modulate sodium and water excretion in the whole kidney.

Our results in isolated renal medulla indicate a very complex interaction between bradykinin and ANP. We obtained a cGMP *vs* ANP curve that is very similar to that shown by others in different *in vitro* preparations, including smooth muscle cells (6), renal epithelial cells (23), rat renal glomeruli (8, 14) and rat renal papillae (14, 22). Noteworthy, the half maximal cGMP production is attained at ANP concentrations around 100 nM, which differs from the dissociation constant (K_d) around 0.05-0.5 nM determined for ANP in binding studies (5, 14).

In contrast to what it may be anticipated, bradykinin –used at concentrations below 1 nM– enhanced rather than inhibited cGMP accumulation induced by ANP. We think that the increased cGMP production in the presence of bradykinin corresponds to a true potentiating effect of bradykinin upon ANP response. We discarded a significant contribution of soluble guanylate cyclase, that may be stimulated by the bradykinin - endothelial nitric oxide pathway (20). This assertion is based on the fact that bradykinin alone did not change renal medullary cGMP content, and direct stimulation of soluble guanylate cyclase with 1 μM sodium nitroprusside produced only a minor cGMP accumulation in comparison with the levels attained after incubation with ANP. Taken together, these data indicate that –in the minced renal medulla– the contribution of soluble guanylate cyclase is negligible in comparison with cGMP produced by the GC-ANP-receptor.

Strikingly, the concentrations of 1-10 nM bradykinin resulted in a lower ANP-induced cGMP production than that attained in the presence of 1-100 pM bradykinin. This effect was observed at two different ANP concentrations. We speculate that *in vivo*, medullary bradykinin concentrations (above

1 pM but below 1 nM) (7), play a permissive role on the response of GC-ANP receptors, allowing for a maximal cGMP production following stimulation by natriuretic peptides at concentrations near their K_d. When bradykinin concentration rises above this level, inhibition of ANP response takes place. Such a mechanism may explain our observations regarding the inhibition of ANP's excretory effect exerted by precise doses of bradykinin in anesthetized rats, and also the results shown here in the isolated rat kidney.

In the presence of HOE-140, bradykinin did not modify ANP induced cGMP production, confirming the specificity of bradykinin effects. However, the kinin antagonist alone produced a stimulatory effect on cGMP accumulation that is difficult to explain. It is possible that 100 nM HOE-140 induced some unknown partial agonistic effect, increasing basal and ANP-stimulated cGMP levels. Further studies utilizing an agonist for B1-bradykinin receptors are needed to clarify this issue.

The possibility of cross-talk between bradykinin and ANP is supported by the fact that the GC-ANP receptor can be modulated by several intracellular signals, and its enzymatic activity is modified by phosphorylation and dimerization (9). While ATP enhances cGMP production induced by ANP, by binding to an intracellular protein-kinase-like domain present in the GC-ANP receptor, stimulation of GC-ANP receptors by ANP is antagonized by activators of protein kinase C (PKC) (9). In membrane preparations of cellular lines over-expressing the GC-ANP receptor, the use of PKC activators and inhibitors has revealed that PKC down-regulates ANP receptor activity, and this effect is counteracted by ATP (23, 25). Thus, a putative explanation for our results is that high levels of bradykinin induce activation of PKC and desensitization of GC-ANP receptor in medullary collecting duct cells, but this hypothesis has to be tested experimentally.

In summary, this work contributes to elucidate the mechanisms of bradykinin-induced inhibition of ANP natriuretic effect by demonstrating that the antagonism can take place directly in the kidney, and also by providing evidence that bradykinin modulates ANP-induced cGMP production in the renal medulla.

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REFERENCES

1 BHOOLA KD, FIGUEROA CD, WORTHY K (1992) Bioregulation of kinins: Kallikreins, kininogens, and kininases. Pharmacol Rev 44: 1-80

2 BORIC M P, CROXATTO HR (1995) Inhibition of atrial natriuretic peptide excretory action by bradykinin. Hypertension 26: 1167-1172

3 BORIC MP, CROXATTO HR, ALBERTINI R, ROBLERO JS (1992) Inhibition of atrial natriuretic peptide-induced natriuresis by plasma hydrolysates containing pepsanurin. Hypertension 19 (Suppl II): II243- II250

4 BORIC MP, CROXATTO HR, MORENO JM, SILVA R, HERNANDEZ C, ROBLERO JS (1998) Kinins mediate the inhibition of atrial natriuretic peptide diuretic effect induced by pepsanurin. Biol Res 31: 33-48

5 BRENNER BM, BALLERMAN BJ, GUNNING ME, ZEIDEL ML (1990) Diverse biological actions of atrial natriuretic peptide. Physiol. Rev. 70: 665-699

6 BUDZIK GP, FIRESTONE SL, BUSH EN, CONNOLLY PJ, ROCKWAY TW, SARIN VK, HOLLEMAN WH (1987) Divergence of ANF analogs in smooth muscle cell cGMP response and aorta vasorelaxation: evidence for receptor subtypes. Biochem Biophys Res Commun 144: 422-431

7 CAMPBELL DJ, KLADIS A, DUNCAN AM (1993) Bradykinin peptides in kidney, blood, and other tissues of the rat. Hypertension 21:155-165

8 CHABARDES D, MONTEGUT M, MISTAOUI M, BUTLEN D, MOREL F (1987) Atrial natriuretic peptide effects on cGMP and cAMP contents in microdissected glomeruli and segments of the rat and rabbit nephrons. Pflügers Arch 408: 366-372

9 CHINKERS M (1996) Molecular genetics and control of atrial natriuretic peptide receptors. Proc Soc Exp Biol Med 213: 105-108

10 CROXATTO H (1957) Polypeptides with posterior pituitary-like activities. In: HELLER H (ed) The Neurohypophysis. London: Butterworths. pp 51-60

11 CROXATTO HR, BORIC MP, ROBLERO JS, ALBERTINI R (1993) Blunting effect of pepsanurin introduced in the duodenum on the atrial natriuretic peptide diuretic action in rats. Proc Soc Exp Biol Med 202: 371-376

12 CROXATTO HR, BORIC MP, ROBLERO JS, ALBERTINI R, SILVA R (1994) Digestive process and regulation of renal excretory function: Pepsanurin and prokinin inhibitors of diuresis mediated by atrial natriuretic peptide. Rev Med Chile 122: 737-745

13 CROXATTO HR, FIGUEROA X, ROBLERO J, ALBERTINI R, SILVA R, BORIC MP (1996) A fragment of human kininogen containing bradykinin blunts the diuretic effect of atrial natriuretic peptide. Proc Soc Exp Biol Med 212: 128-134
14 DE LEON H, BONHOMME MC, GARCIA R (1994) Rat renal preglomerular vessels, glomeruli and papillae do not express detectable quantities of B-type natriuretic peptide receptor. J Hypert 12: 539-548
15 FIGUEROA CD, GONZALEZ CB, GRIGORIEV S, ABDALLA S, HAASEMANN M, JARNAGIN K, MÜLLER-ESTERL W (1995) Probing for the bradykinin B2 receptor in rat kidney by anti-peptide and anti-ligand antibodies. J Histochem Cytochem 43: 137-148
16 GAILLARD CA, KOOMANS HA, DORHOUT MEES EJ (1988) Enalapril attenuates natriuresis of atrial natriuretic factor in humans. Hypertension 11:160-165
17 GERZER R, HEIM JM, SCHÜTTE B, WEIL J (1987) Cellular mechanisms of action of atrial natriuretic factor. Klin Wochenschr 65 (Suppl VIII): 109-114
18 HOCK FJ, WIRTH K, ALBUS U, LINZ W, GERHARDS HJ, WIEMER G, BREIPOHL G, KONIG W, KNOLLE J, SCHOLKENS BA (1991) HOE-140 a new potent and long acting bradykinin antagonist. *In vitro* studies. Br J Pharmacol 102: 769-773
19 MAACK T, NIKONOVA LN, FRIEDMAN O, COHEN D (1996) Functional properties and dynamics of natriuretic peptide receptors. Proc Soc Exp Biol Med 213: 109-116
20 MOMBOULI JV, VANHOUTTE PM (1995) Kinins and endothelial control of vascular smooth muscle. Annu Rev Pharmacol Toxicol 35: 679-705
21 MOTWANI JG, LANG CC, CRAMB G, STRUTHERS AD (1995) Natriuretic response to endopeptidase inhibition is blunted by enalapril in healthy men. Hypertension 25: 637-642
22 NUGLOZEH E, GAUQUELIN G, GARCIA R, TREMBLAY J, SCHIFFRIN EL (1990) Atrial natriuretic peptide receptors in renal papilla of DOCA-salt hypertensive rats. Am J Physiol 259: F130-F137
23 POTTERS LR, GARBERS DL (1994) Protein kinase C-dependent desensitization of the atrial natriuretic peptide receptor is mediated by dephosphorylation. J Biol Chem 269: 14636-14642
24 SALAS SP, ROBLERO JS, LOPEZ LF, TACHIBANA S, HUIDOBRO-TORO JP (1992) [N-Methyl-Tyr1,N-Methyl-Arg7-D-Leu8]-dynorphin-A-(1-8)Ethylamide, a stable dynorphin analog, produces diuresis by kappa-opiate receptor activation in the rat. J Pharmacol Exp Ther 262: 979-986
25 SHIGEMATSU Y, VAUGHN J, FROHLICH ED, COLE FE (1993) Adenosine 5′-triphosphate, phorbol ester, and pertussis toxin effects on atrial natriuretic peptide stimulation of guanylate cyclase in a human renal cell line. Life Sci 54: 213-221
26 SIRAGY HM, IBRAHIM MM, JAFFA AA, MAYFIELD R, MARGOLIUS HS (1994) Rat renal interstitial bradykinin, prostaglandin E2, and cyclic guanosine 3',5'-monophosphate. Effects of altered sodium intake. Hypertension 23: 1068-1070
27 SIRAGY HM, JAFFA AA, MARGOLIUS HS, CAREY RM (1996) Renin-angiotensin system modulates renal bradykinin production. Am J Physiol 271: R1090-R1095
28 TERADA Y, MORIYAMA T, MARTIN BM, KNEPPER MA, GARCIA-PEREZ A (1991) RT-PCR microlocalization of mRNA for guanylyl cyclase-coupled ANP receptor in rat kidney. Am J Physiol 261: F1080-F1087
29 VALDIVIESO A, BORIC MP, RIQUELME A, ROBLERO J (1993) Renal vascular and excretory resistance to atrial natriuretic peptide in pre-cirrhotic, bile-duct ligated rats. Biol Res 26: 397-404
30 VIO CP, LOYOLA S, VELARDE V (1992) Localization of components of the kallikrein-kinin system in the kidney: relation to renal function. Hypertension 19 (Suppl II): II10-II16
31 VIO CP, VELARDE V, MÜLLER-ESTERL W (1996) Cellular distribution and fate of the bradykinin antagonist HOE 140 in the rat kidney. Colocalization with the bradykinin B2 receptor. Immunopharmacology 33: 146-150
32 WAMBACH G, SCHITTENHELM U, STIMPEL M, BONNER G, KAUFMANN W (1989) Natriuretic action of ANP is blunted by ACE inhibition in humans. J Cardiovasc Pharmacol 13:748-753
33 WIRHT KJ, BICKEL M, HROPOT M, GÜNZLER V, HEITSCH H, RUPPERT D, SCHÖLKENS BA (1997) The bradykinin B2 receptor antagonist Icatibant (HOE 140) corrects avid Na^+ retention in rats with CCl_4-induced liver cirrhosis: possible role of enhanced microvascular leakage. Eur J Pharmacol 337: 45-53
34 ZEIDEL ML (1990) Renal actions of atrial natriuretic peptide: regulation of collecting duct sodium and water transport. Annu Rev Physiol 52: 747-759
35 ZEIDEL ML (1993) Hormonal regulation of inner medullary collecting duct sodium transport Am J Physiol 265: F159-F173