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Effects of Atrial Natriuretic Peptide during Angiotensin Converting-Enzyme Inhibition in the Anesthetized Rat

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ABSTRACT

The contribution of the renin–angiotensin system to the depressor and natriuretic responses to intravenous infusion of synthetic atrial natriuretic peptide (ANP; 0.1 and 1 μg/kg/min, 45 min each) was determined in euvolemic anesthetized untreated rats and in captopril-pretreated animals. In untreated rats, ANP infusion was associated with no change in mean arterial pressure during the low dose infusion (LD) and a 20 mmHg decrease during the high dose infusion (HD) from a basal value of 111±4 mmHg. ANP induced a dose-dependent increase in urinary sodium excretion (UNaV; from 0.48±0.07 to 1.28±0.33 and 3.12±0.88 μeq/min), fractional excretion of lithium (from 21.9±3.3 to 27.3±2.5 and 32.9±3.5%), and a decrease in fractional distal reabsorption of sodium. These changes were reversed after discontinuation of ANP infusion. Glomerular filtration rate (GFR) was unaltered whereas effective renal plasma flow (ERPF) decreased only during HD; filtration fraction (FF) increased in a dose dependent manner in response to ANP infusion. When the renin–angiotensin system was blocked by capopril (50 mg/dl of drinking water for 6 weeks), baseline pressure was 90±3 mmHg and fell subsequently to 85±3 and 69±4 during LD and HD respectively. In captopril-pretreated animals, the natriuretic response to ANP infusion was preserved during LD (from 0.96±0.18 to 1.6±0.36 μeq/min) but was significantly attenuated during HD (2.27±0.70 μeq/min) as was the fractional excretion of lithium (from 18.3±2.6 to 25.7±2.3 and 18.5±3.5%). ANP induced changes in renal hemodynamic were preserved in captopril pretreated animals as was the decrease in fractional distal reabsorption of sodium. In conclusion, converting enzyme inhibition induced by captopril does not interfere with the hypotensive response to ANP but attenuates it's natriuretic action. This latter effect can be due to the blood pressure lowering effect of captopril or alternatively to an interaction between angiotensin II and ANP at the level of the proximal tubule.

INTRODUCTION

Atrial natriuretic peptide (ANP) is a circulating hormone synthetized in, stored in, and released from cardiac atria which possesses diuretic and natriuretic properties (Brenner et al., 1990). ANP may also play a role as a regulator of the extracellular fluid volume and arterial blood pressure (Brenner et al., 1990).

The renin–angiotensin system is geared to sodium conservation. Infusion of ANP also suppresses the renin–angiotensin system and numerous studies have reported on ANP antagonization of the renin–angiotensin system at various levels (Johnston et al., 1989; Brenner et al., 1990). In fact, it has been suggested that ANP inhibits renin secretion (Burnett et al., 1984) as well as the effects of angiotensin II on aldosterone secretion (Anderson et al., 1986), vascular resistance (Lappe et al., 1987) and angiotensin-stimulated sodium and water transport at the level of the proximal tubule (Harris et al., 1987). Since angiotensin II produces vasoconstriction and enhanced sodium reabsorption, the depressor and natriuretic effects of ANP may be due in part to inhibition of the renin system.

In the present study, the renal and systemic responses to intravenous administration of increasing doses of ANP were determined in anesthetized rats chronically pretreated with the converting enzyme inhibitor captopril, which blocks the conversion of angiotensin I to angiotensin II (Rubin et al., 1978). If a decrease in the activity or concentration of angiotensin II is an effector mechanism for ANP, an impaired natriuretic and/or hypotensive responses to ANP infusion in rats pretreated with captopril would be expected.

METHODS

Studies were conducted in male Sprague–Dawley rats (Charles-River, France), weighing 380–450 g and allowed free access to food and water until the day of experimentation. Ten rats received captopril (Squibb and Sons, Princeton, NJ) dissolved in the drinking water at a dose of 50 mg/100 ml for 6 weeks prior to experiments. On the day of the experiment,

the animals were given lithium chloride (0.5 mmol/kg) by gavage 90 minutes prior to anesthesia (Inactin 100 mg/kg ip, Byk-Gulden, Germany) and then placed on a temperature regulated table to maintain rectal temperature at 37±0.5°C. Rats were tracheotomized to allow spontaneous breathing and prepared for acute experimentation as previously described (Valentin et al., 1990). Briefly, catheters were inserted into a femoral artery, a femoral vein, a carotid artery and the right jugular vein for sampling blood, infusing solutions and continuously measuring arterial and right atrial pressures respectively (Statham P50 pressure transducers connected to a Gould recorder). A PE-60 catheter was inserted into the dome of the urinary bladder via a midline suprapubic incision for urine collections. During the surgical preparation, a solution containing 3% bovine serum albumin (Sigma Chemical, St. Louis, MO) in saline was infused to replace fluid losses up to a total volume of 1.25% of body weight. After completion of surgery, albumin infusion was discontinued and replaced by a solution of 0.9% sodium chloride containing the radioactive tracers used for clearance studies (40 μl/min throughout the remainder of the experiment). After a 45-min equilibration period, 3 control urine collections of 20 min each were obtained (basal period), the rats then received hANP (103–126; Wyeth Lab. 47.663) at 0.1 μg/kg/min for 45 min followed by 1 μg/kg/min for another 45 min. At the end of the ANP infusion period a 45-min period was allowed for recovery (recovery period). At the midpoint of each clearance period, a blood sample (150–180 μl) was drawn. After centrifugation, plasma was saved and stored for future analysis; red blood cells were resuspended in an equal volume of normal saline and injected back to the animal via the femoral vein. Urine was collected under water-equilibrated mineral oil in weighed plastic vials; urine volume was determined from urine weight and specific gravity measured with an eye-piece refractometer (Atago, Japan). At the end of each experiment, the efficacy of angiotensin converting-enzyme inhibition was confirmed by the determination of the pressor response to a bolus injection of 200 ng of angiotensin I (Sigma, St. Louis, MO).

Analytical techniques and statistical evaluation

The analytical techniques employed have been previously detailed (Valentin et al., 1990). Briefly, hematocrit (Hct) was determined in triplicate on each blood sample by spinning blood at 12,000 rpm in a microfuge (Hettich Haematokrit, Germany). Plasma protein concentration was measured by refractometry (Atago, Japan). Plasma and urine sodium and potassium were determined by flame photometry. Lithium in plasma and urine was determined by atomic absorption spectrophotometry. Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were estimated by clearances of ^{99m}Tc-diethylenetriaminepenta-acetic acid (DTPA) and sodium ^{131}I-orthoiodohippurate, respectively. Renal blood flow was calculated as ERPF/(1-Hct) and renal vascular resistance as mean arterial pressure (MAP)/renal blood flow. Clearances of sodium (CNa) and potassium (CK) were calculated according to standard formula, and fractional excretions of Na and K were calculated as (CNa/GFR)×100 and (CK/GFR)×100, respectively. The fractional excretion of lithium (CLi/GFR)×100 was used as an index of whole kidney proximal tubular reabsorption (Koomans et al., 1989). Fractional distal reabsorption of sodium was calculated as (1–(CNa/CLi))×100. Since previous experiments demonstrated no differences in renal function between the right and left side, as estimated by separate ureteral catheterization (Ribstein and Humphreys, 1983), values were expressed for a single kidney by halving the total kidney function. The results of all clearance measurements were averaged to provide a single value for the basal, the low and high dose infusion of ANP, and for the recovery period for each rat. Data are expressed as means±SEM. Two-way analysis of variance and Student's *t* test, with correction for multiple comparison when indicated, were used to assess significance among and between groups. A P value of 0.05 was considered the minimum level of significance.

RESULTS

Systemic and renal effects of ANP

The stability of systemic and renal parameters over time has been previously reported (Valentin et al., 1990). As depicted in Fig. 1, infusion of ANP in untreated rats was associated with no change in arterial pressure at the low dose and a significant ($P<0.05$) decrease at the high dose (from 111±4 to 109±5 and 89±3 mmHg), and right atrial pressure decreased in a dose dependent manner. As shown in Fig. 2, ANP infusion produced a dose-dependent rise in urine flow rate (UV) by 55±24 and 394±231% for the low and high dose respectively from a basal value of 7±1.1 μl/min. As also presented in Fig. 2, urinary sodium excretion (UNaV) rose from 0.48±0.07 to 1.28±0.33 at the lower dose and further to 3.12±0.88 μeq/min at the higher dose of ANP (both $P<0.05$ vs. control period). The increase in UV and UNaV were reversed after discontinuation of the drug infusion. No significant change in potassium excretion (UKV) was observed over time (from 0.70±0.14 to 0.78±0.14

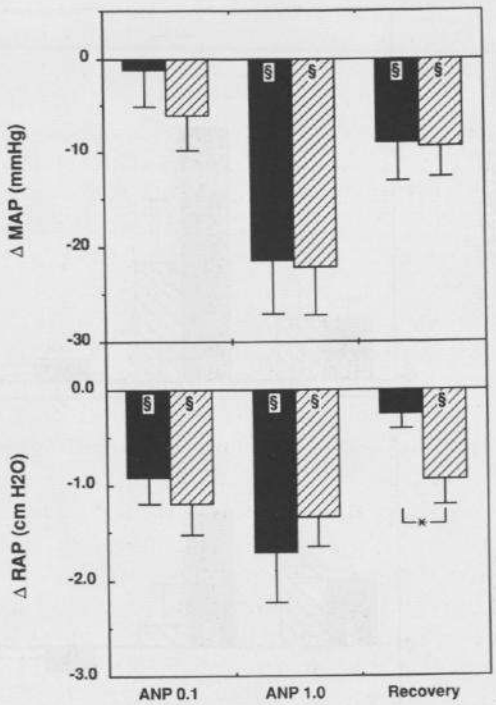

Fig. 1. Effect of intravenous infusion of ANP on absolute changes of mean arterial pressure (ΔMAP, top panel) and right atrial pressure (ΔRAP, bottom panel) in untreated rats (black histogram; n=10) and in captopril-pretreated animals (hatched histogram; n=10). ANP was infused at 0.1 μg/ kg/min for 45 min followed by 1 μg/kg/min for another 45 min. §Significant changes (P<0.05) from baseline; *significantly different between groups.

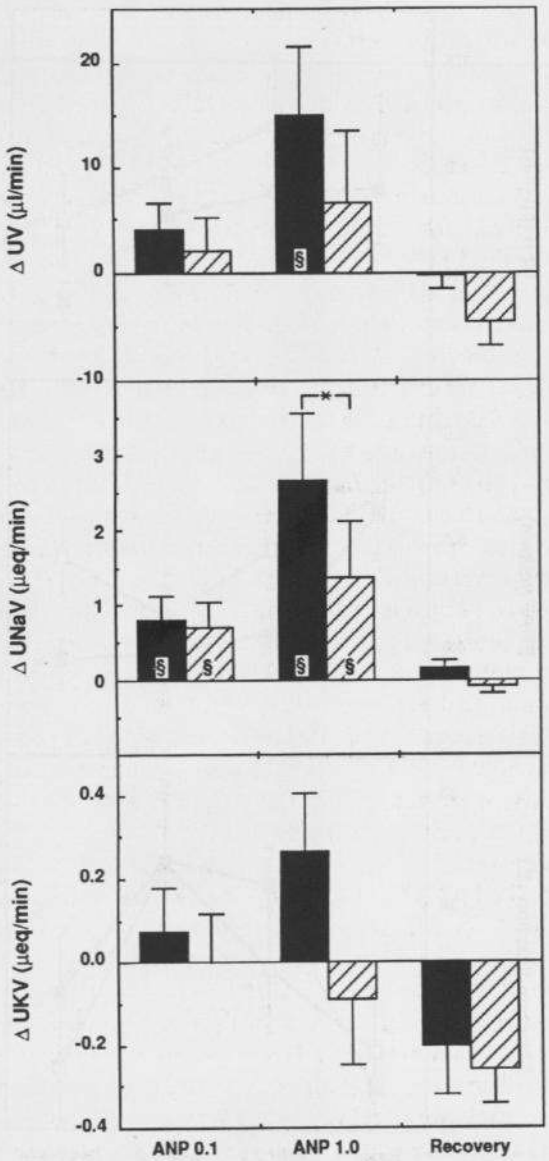

Fig. 2. Effect of intravenous infusion of ANP on absolute changes of urine flow rate (ΔUV, top panel), sodium excretion (ΔUNaV, middle panel) and potassium excretion (ΔUKV, bottom panel) in untreated rats (black histogram) and in captopril-pretreated animals (hatched histogram). ANP was infused at 0.1 μg/ kg/min for 45 min followed by 1 μg/kg/min for another 45 min. §Significant changes (P<0.05) from baseline; *significantly different between groups.

and 0.97±0.11 μeq/min) (Fig. 2). As shown in Fig. 3, GFR was unaltered (from 1.36±0.08 to 1.39±0.12 and 1.30±0.09 ml/min), while ERPF decreased in a dose dependent fashion (from 5.43±0.51 to 4.94±0.35 and 4.29±0.31 ml/min) and as a consequence, filtration fraction (FF) increased dose-dependently in response to ANP (from 26.1±1.7 to 28.3±1.7 and 31.1± 1.9%). RVR did not change significantly throughout the experiment as a consequence of the parallel evolution of MAP and renal blood flow. The increase in FENa (from 0.24±0.04 to 0.57±0.12 and 1.61±0.39%) was associated with a dose-dependent and reversible increase in the fractional excretion of lithium (FELi) (from 21.9±3.3 to 27.3±2.5 and 32.9±3.5%) and a reduction in the fractional distal reabsorption of sodium (FDRNa) (from 98.9±0.1 to 97.8±0.5 and 94.8±1.5%) (Fig. 4). Hematocrit and plasma protein concentration did not change significantly over the duration of the experiment.

Effect of Captopril-pretreatment on basal values

The efficacy of angiotensin converting-enzyme inhibition was assessed in each experiment. The pressor response (+36±3 mm Hg) to a bolus injection of angiotensin I observed in untreated rats was significantly (p<0.005) attenuated in captopril-pretreated rats (+2.4±0.7 mm Hg). Analysis of variance indicates that angiotensin converting-enzyme inhibition was associated with a reduction in MAP and no significant change in renal hemodynamic (Table 1). Captopril-pretreatment also resulted in an increase in water and sodium excretion as well as a significant reduction in fractional distal reabsorption of sodium (Table 1).

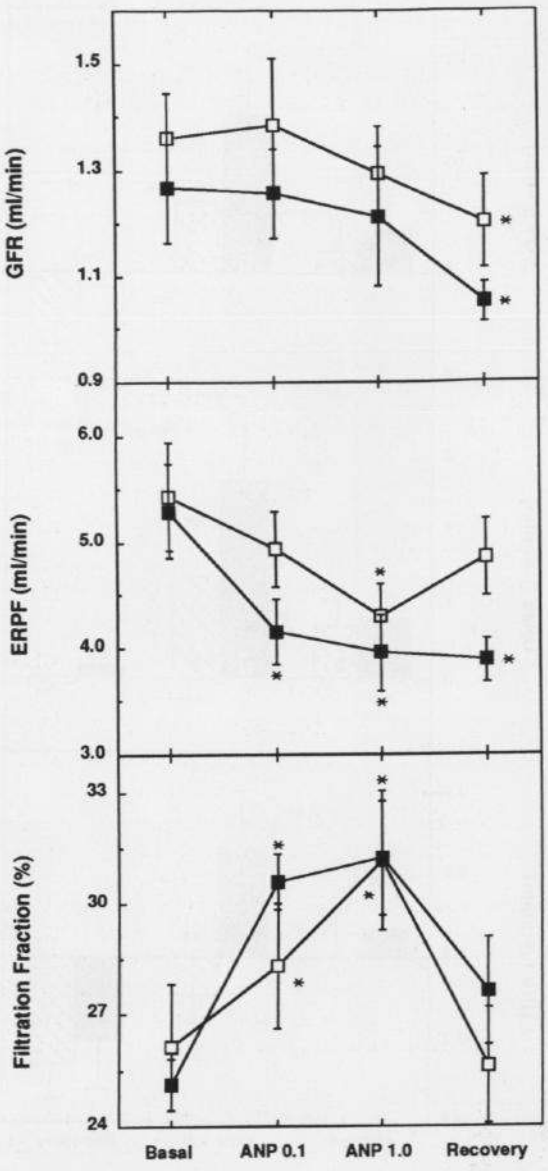

Fig. 3. Effect of intravenous infusion of ANP on changes of glomerular filtration rate (GFR, top panel), effective renal plasma flow (ERPF, middle panel) and filtration fraction (bottom panel) in untreated rats (black histogram) and in captopril-pretreated animals (hatched histogram). ANP was infused at 0.1 μg/ kg/min for 45 min followed by 1 μg/kg/min for another 45 min. *Significant changes ($P<0.05$) from baseline.

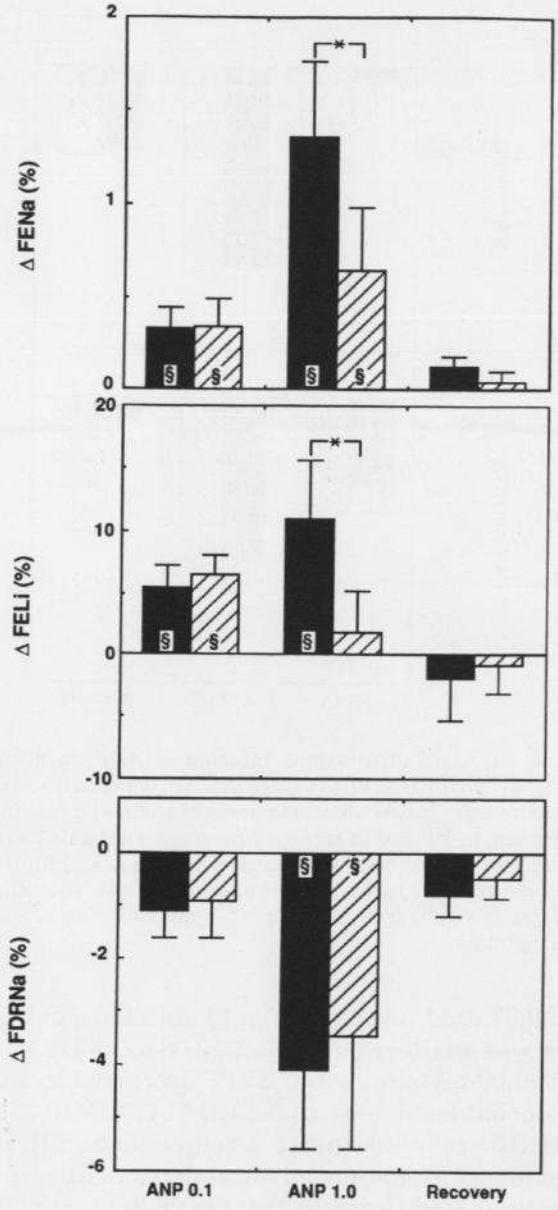

Fig. 4. Effect of intravenous infusion of ANP on percent changes of fractional excretion of sodium (ΔFENa, top panel), lithium (ΔFELi, middle panel) and fractional distal reabsorption of sodium (ΔFDRNa, bottom panel) in untreated rats (black histogram) and in captopril-pretreated animals (hatched histogram). ANP was infused at 0.1 μg/ kg/min for 45 min followed by 1 μg/kg/min for another 45 min. §Significant changes ($P<0.05$) from baseline; *significantly different between groups.

Influence of Captopril-pretreatment on the responses to ANP

The decrease in MAP observed in captopril-pretreated rats (from 90±3 to 85±3 and 69±4 mm Hg) was similar to that observed in untreated rats (Fig. 1). As observed in untreated animals, hematocrit and plasma protein concentration did not change significantly over time and right atrial pressure decreased dose-dependently. The absolute increase in UV of 6.7±6.9 μl/min observed at the high dose of ANP was attenuated as compared to the increase seen at the same dose in untreated animals (Fig. 2). UNaV increased from 0.96±0.18 to 1.60±0.36 at the low dose and further to 2.27±0.70 μeq/min at the high dose respectively. This increase of 1.4±0.7 μeq/min at the high dose was significantly less than that (2.6±0.9 μeq/min) observed at the same dose in untreated rats (Fig. 2). The increase in UKV observed in untreated animals was not noted over time in captopril-pretreated animals. As shown in Fig 4.,

in captopril-pretreated rats FELi increased only at the low dose while the decrease in FDRNa was comparable to that observed in untreated animals.

DISCUSSION

A number of investigators have reported that synthetic ANP simultaneously increases sodium excretion and suppresses renin secretion and aldosterone production despite a concurrent reduction in MAP (Burnett et al., 1984; Maack et al., 1984; Seymour and Mazack, 1988; Johnston et al., 1989; Brenner et al., 1990). Because the effectors of the renin–angiotensin–aldosterone cascade (angiotensin II and aldosterone) produce vasoconstriction and enhance tubular sodium reabsorption, lowering the endogenous activity of the renin system could contribute to the cardiovascular and renal responses to ANP.

In the present study, we evaluated the importance of the renin–angiotensin system to the natriuretic and depressor responses to ANP in euvolemic anesthetized rats. Results showed that when the renin–angiotensin system is impaired by chronic administration of captopril, the natriuretic response to ANP is significantly attenuated at the high dose of infusion while the hypotensive response is still present.

The hypotensive effect of ANP was not abolished in the captopril pretreated animals, but was exactly equal to that seen in untreated animals (20 mm Hg at the high dose). This observation is in agreement with previous work of Hansell and Ulfendahl (1987) in anesthetized rats using acute inhibition by captopril and that of Seymour and Mazack (1988) in anesthetized dogs using acute inhibition by enalaprilat. These observations suggest that angiotensin II is not involved in the ANP-mediated hypotension. However, not all studies could confirm this observation (Di Nicolantonio et al., 1986; 1987).

It is evident from our results that the natriuretic response to ANP can occur without a sustained increase in GFR, which support the view that the tubular action of ANP plays a major role in its natriuretic action. Since in euvolemic rats, changes in the tubular handling of lithium closely reflect changes in the proximal tubular reabsorption of sodium (Koomans et al., 1989), the present findings suggest that the natriuretic response to ANP administration results at least in part from a decrease in the proximal reabsorption of sodium. In fact, it has been proposed that ANP, in addition to its well documented inhibition of distal sodium reabsorption (Brenner et al., 1990; Zeidel, 1990), may also decrease proximal tubular reabsorption of solutes such as phosphate (Hammond et al., 1985a), bicarbonate (Hammond et al., 1985b) or lithium (Burnett et al., 1984).

The observation that ANP and angiotensin II have strikingly opposite effects on blood pressure and fluid volume regulation has led to speculation regarding the possible physiologic relevance of this antagonism (Johnston et al., 1989; Raine et al., 1989). Our results indicate that the dose-dependent decrease in fractional distal reabsorption of sodium following ANP infusion is still observed in captopril-pretreated rats; thus suggesting that the direct effect of ANP on inhibition of distal sodium reabsorption is preserved in these animals. In contrast, the blunted natriuretic response observed at the high dose of ANP in captopril-pretreated rats is associated with a significant attenuation of the increase in the fractional excretion of lithium; thus suggesting that an alteration of the proximal reabsorption of sodium may be responsible for the observed blunted natriuresis in captopril-pretreated rats. It has been observed that angiotensin II may modulate the intrarenal effects of ANP (Siragy et al., 1988). In fact, it has been shown that ANP may blunt angiotensin II-stimulated sodium and water trans-

TABLE 1

Baseline values for renal and systemic hemodynamic and electrolyte excretion in untreated rats and in captopril-pretreated rats

	Untreated	Captopril-pretreated	
Number	10	10	
Body weight (g)	427±7	394±10	NS
Hematocrit (%)	44.3±0.7	43.6±0.8	NS
PPC (g/dl)	5.39±0.18	5.17±0.18	NS
MAP (mmHg)	111±4	90±3	<005
UV (μl/min)	7.1 ±1.1	10.3±2.0	NS
UNaV (μeq/min)	0.48±0.07	0.96±0.18	<0.05
UKV (μeq/min)	0.70±0.14	0.68±0.07	NS
GFR (ml/min)	1.36±0.08	1.27±0.1	NS
ERPF (ml/min)	5.43±0.51	5.3±0.45	NS
FF (%)	26.1±1.7	25.1±0.7	NS
RVR (mmHg·min/ml)	12.0±1.0	13.5±2.4	NS
CLi (ml/min)	0.29±0.04	0.27±0.03	NS
FENa (%)	0.24±0.04	0.60±0.13	<0.05
FEK (%)	13.39±2.96	13.95±1.66	NS
FELi (%)	21.94±3.31	18.28±2.57	NS
FDRNa (%)	98.86±0.12	96.59±0.79	<0.05

Values are means±SEM of 3 clearance periods for one kidney during basal period. PPC, plasma protein concentration; MAP, mean arterial pressure; UV, urine flow; UNaV and UKV, urinary sodium and potassium excretion; GFR, glomerular filtration rate; ERPF, effective renal plasma flow; FF, filtration fraction; RVR, renal vascular resistance; CLi, lithium clearance; FENa, FELi and FEK, fractional excretion of sodium, potassium and lithium; FDRNa, fractional distal reabsorption of sodium. *P<0.05 between groups. NS, not significant.

port in the proximal tubule (Harris et al., 1987). Such an antagonism may account for our specific observation. Alternatively, because chronic treatment by captopril alone reduced blood pressure, a condition that normally attenuates natriuresis (Seymour et al., 1987), we could not conclude that inhibition of the renin–angiotensin system *per se* was responsible for the effects of captopril. However, the natriuretic effect of ANP is still preserved at the low dose despite a blood pressure significantly reduced in captopril treated animals as compared to untreated animals (85±3 vs. 109±5 mm Hg).

Angiotensin II is known to stimulate aldosterone production (Anderson et al., 1986; Johnston et al., 1989; Brenner et al., 1990); therefore, the suppression of the angiotensin II generation by captopril as used in our experiments may decrease basal production of aldosterone thus resulting in a decrease in the fractional distal reabsorption of sodium and an increase in the fractional excretion of sodium at baseline, as observed in our study. ANP has been shown to inhibit aldosterone production (Johnston et al., 1989; Brenner et al., 1990). The possibility that the decrease in fractional distal reabsorption of sodium observed after ANP infusion could be under the dependence of aldosterone can be ruled out since the decrease in fractional distal reabsorption of sodium was of similar magnitude in untreated and captopril-pretreated rats.

CONCLUSION

In conclusion, the present studies indicate that converting enzyme inhibition induced by captopril does not interfere with the hypotensive response to ANP but attenuates it's natriuretic action. This latter effect may be due to the blood pressure lowering effect of captopril or alternatively to a direct interaction between angiotensin II and ANP at the level of the proximal tubule.

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