Atrial Natriuretic Factor Modulates Proximal Glomerulotubular Balance in Anesthetized Rats

Jialong Zhuo, Peter J. Harris, and Sandford L. Skinner

The extent to which the natriuretic effect of a prolonged low dose infusion of atrial natriuretic factor (30 ng/kg/min) is dependent on interference with the prevailing intrarenal actions of angiotensin II was examined before and after blockade of angiotensin production with the converting enzyme inhibitor enalaprilat (5 mg/kg). Lithium clearance was used to assess proximal tubular sodium and water reabsorption. Atrial natriuretic factor and enalaprilat caused similar increases in sodium excretion (10-fold and sevenfold, respectively) and glomerular filtration rate (each 34%) and similar decreases in fractional proximal reabsorption of sodium (17% and 13%, respectively) and blood pressure. Each also caused a major disruption in the effectiveness of proximal glomerulotubular balance (30% and 50% of perfect balance). Infusion of atrial natriuretic factor during converting enzyme inhibition increased glomerular filtration rate further by 23%, reaching 63% above control without change in renal blood flow but with a rise in filtration fraction to 0.48. Sodium excretion increased further but fractional proximal sodium reabsorption remained constant and proximal glomerulotubular balance appeared to improve. Atrial natriuretic factor therefore possesses a glomerular action that persists during converting enzyme inhibition and is indeed additive to the removal of angiotensin II when the proximal effect of atrial natriuretic factor is no longer apparent. It is concluded that failure of atrial natriuretic factor to further suppress fractional proximal sodium reabsorption during converting enzyme inhibition is caused by either prior removal of the stimulatory action of angiotensin II on proximal tubular transport or extreme changes in peritubular physical factors consequent on the high filtration fraction. (Hypertension 1989;14:666–673)

Controversy exists over whether atrial natriuretic factor (ANF) promotes sodium excretion entirely as a consequence of its ability to increase glomerular filtration rate (GFR)1-3 or additionally by inhibition of tubular reabsorption.4-8 Recent evidence indicates that increased GFR is not necessary for natriuresis.9 Decreased fractional proximal reabsorption, as measured by lithium clearance, has been reported in rats,8,10 dogs,11,12 and humans13,14 after infusion of high or low doses of ANF, although several micropuncture studies have failed to demonstrate a proximal site of action of ANF.5,15,16 Other nonglomerular actions of ANF include inhibition of sodium transport in the medullary collecting duct17,18 and suppression of renin release,11,19 both effects likely to contribute to increased sodium excretion.

Specific, high affinity binding of radiolabeled ligands indicates the presence of ANF receptors associated with glomeruli, inner and outer medulla, and cortical tubules.20-22 In most of these cell types cyclic guanosine 3',5'-monophosphate (cGMP) has been reported to increase in response to ANF 18-23-24 and is presumed to be an intracellular second messenger. The proximal tubule appears to differ because, except for inhibition of sodium-coupled bicarbonate and phosphate transport in proximal brush-border membrane vesicles,25 most studies show that ANF has no direct action on proximal tubule sodium transport7,26-28 and does not stimulate cGMP in these cells.24,29 However, if proximal sodium reabsorption is first stimulated by angiotensin II, subsequent peritubular addition of ANF reveals a dose-dependent inhibitory action.7

Similarly, although it is well recognized that high doses of ANF cause hyperfiltration associ-
ated with increased production of glomerular cGMP, the specific physical and cellular mechanisms of hyperfiltration remain to be elucidated. In isolated rabbit glomerular arterioles in vitro, atriopeptin II had no effect on afferent or efferent arteriole diameter in either relaxed vessels or after constriction with noradrenaline or angiotensin II. However, ANF in vivo dilated pregglomerular vessels and caused efferent vasoconstriction. In addition, ANF may affect mesangial, visceral epithelial, or endothelial cells leading to an altered ultrafiltration coefficient \( (K_f) \).

In anesthetized rats, we have found that the normal effectiveness of proximal glomerulotubular balance (i.e., the relation of the volume of proximal reabsorbate to filtrate) is dependent on the presence of angiotensin II and is impaired during hyperfiltration due to ANF but not glucagon. Furthermore, in recent micropuncture experiments the proximal tubular action of ANF appears to be exerted only through antagonism of angiotensin II–stimulated sodium transport. In humans and in anesthetized dogs, clearance studies indicate that at least part of the natriuretic activity of ANF is dependent on angiotensin II, although the quantitative importance of this interaction under normal conditions has been questioned. We have therefore examined the effects of ANF on filtration, reabsorption, and excretion of sodium and water in intact kidneys in anesthetized rats in the presence of angiotensin II and during inhibition of converting enzyme with enalaprilat. Comparison between lithium and inulin clearances was used as a measure of proximal sodium and water reabsorption.

Materials and Methods

Animal Preparation

Sixteen male Long Evans rats weighing 250–280 g were used and prepared as previously described. Rats were maintained on a normal laboratory diet (Barastoc Stock Feeds, Melbourne, Victoria, Australia) and permitted free access to tap water until 2 days before experimentation. Each rat was then caged individually and fed a wet mash diet with 15 mmol lithium chloride and 100 mmol sodium chloride/kg dry food. With this dietary treatment, the nphrotoxic effects of high lithium concentration on the kidneys are avoided, but the concentration of lithium in plasma and urine samples can be measured accurately. In addition, the sodium intake of the animals is well in excess of that required to reduce distal reabsorption of lithium to a negligible level.

At the start of experimentation, the rats were anesthetized with Inactin (110 mg/kg body wt i.p.) (BYK Gulden, Konstanz, FRG) and placed on a thermostatically controlled heated table. Body temperature was maintained stable at 37° C and tracheostomy performed. Two cannulae (SP-35) were inserted into the jugular veins for infusions of 0.9% NaCl (saline), clearance markers, and drugs. Saline infusion commenced immediately after insertion of the cannulae. A third cannula (SP-35) was placed in the right carotid artery for blood sampling and connected to a pressure transducer (model P23Db, Statham Instrs. Division, Gould Inc., Oxnard, California) and chart recorder (Type RB Dynograph, Beckman Instrs., Inc., Chicago, Illinois) to record mean arterial blood pressure. Urine samples were collected under paraffin oil in preweighed tubes through a cannula placed in the bladder via a suprapubic midline incision.

On completion of surgical procedures, a priming dose (0.4 ml) containing 8% polyfructosan (Inutest, Laevosan-Gesellschaft, Linz, Donau, Austria) and 1% p-aminohippuric acid (Sigma Chemical Co., St. Louis, Missouri) was given via jugular vein and followed by a sustaining infusion of 8% polyfructosan and 1% p-aminohippuric acid in saline at the rate of 0.0375 ml/min. Lithium chloride (4 mmol/l in saline) was then infused from a second syringe at 0.0375 ml/min throughout each experiment. Plasma lithium concentrations were in the range 0.15–0.25 mmol/l. A 120-minute equilibration period was allowed before the experimental protocol was commenced.

Experimental Protocol

After the equilibration period, rats were allocated to two groups and, initially, subjected to similar control periods in which urine samples were collected during three 20-minute periods. The control period was followed by three 60-minute experimental periods during which three 20-minute urine collections were made with arterial blood sampling (0.4 ml) at the midpoint of each 60-minute period. Hematocrit was estimated, and the plasma was stored frozen for later measurement of electrolytes and renal clearance markers. The blood cells were resuspended in 0.2 ml saline and returned to the rat via a jugular cannula. At the end of the experiment, the kidneys were removed, blotted, and weighed. Rats in group 1 were given converting enzyme inhibitor (CEI) only. Rats in group 2 received CEI as for group 1 and were then infused with ANF. All rats received the same total and constant rate of volume infusion (0.075 ml/min).

Group 1 (n=8). On completion of the control period, a single intravenous dose (5 mg/kg body wt) of enalaprilat (MK422, Merck, Sharp & Dohme, Rahway, New Jersey) was injected. A period of 30 minutes was then allowed for full development of the effects of converting enzyme inhibition. Three 60-minute experimental periods were then observed and designated “CEI” with 30-minute intervals between each. The effectiveness of converting enzyme inhibition was checked by abolition of the pressor response to injection of 5 ng angiotensin I in 50 μl saline given before and then 30 minutes after administration of enalaprilat, as well as at the end of each experiment.
Group 2 (n=8). Rats in this group were treated identically to those in group 1, except that in the second experimental period ("CEI+ANF") during continuing converting enzyme inhibition, a constant intravenous infusion of ANF (synthetic α-rANP$_{1-23}$, Ciba-Geigy, Basel, Switzerland) was introduced at the rate of 10 ng/min (average 30 ng/kg/min) added to the lithium chloride infusion. Urine collections were recommenced 30 minutes after the start and termination of ANF infusion. Time control studies appropriate for these protocols have been published elsewhere.

Analytical Methods

Urine volume was determined gravimetrically and hematocrit measured by the microcapillary method. Sodium and potassium concentrations in plasma and urine samples were measured by flame photometry (model IL943, Instrumentation Laboratories, Lexington, Massachusetts) and lithium concentrations in plasma and urine by using atomic absorption spectrophotometry (model 901, GBC Scientific, Melbourne, Australia). Polyfructosan concentrations were estimated with the anthrone method and $p$-aminohippuric acid as described by Smith et al.

Calculations

Clearances of polyfructosan and $p$-aminohippuric acid were calculated by using the standard clearance equation and taken as indexes of GFR and renal plasma flow, respectively. It was assumed that $p$-aminohippuric acid extraction remained constant at 90%. Lithium clearance ($C_L$) was calculated in the same way and taken to represent filtrate delivery from the end of the proximal tubule into the diluting segment in the whole kidney nephron population. Fractional proximal reabsorption of sodium ($FPR_{Na}$) and water was calculated from fractional urinary sodium excretion ($FE_{Na}$) to derive fractional distal reabsorption of sodium ($FDR_{Na}$) as described by Thomsen. Total absolute proximal reabsorption ($APR$) of sodium and water was calculated as:

$$APR = GFR - C_L$$

The effectiveness of proximal glomerular tubular balance (GTB) was estimated in response to a change in GFR as:

$$\frac{\% \text{ change in APR} \times 100}{\% \text{ change in GFR}}$$

Statistical Analysis

Values are presented as mean±SEM. Differences between control and experimental periods were analyzed within each group of rats by using the paired Students $t$ test and between each group by unpaired $t$ test. $p<0.05$ was required to achieve statistical significance.

Results

Administration of enalaprilat (CEI) alone induced significant renal vasodilatation and hyperfiltration (Figure 1). In the first experimental period, renal plasma flow increased by 26% in group 1 (from 3.67±0.10 to 4.62±0.13 ml/g kidney wt/min, $p<0.001$) and 29% in group 2 (from 3.71±0.16 to 4.79±0.13 ml/g kidney wt/min, $p<0.001$). GFR increased by 34% in group 1 (from 3.67±0.10 to 4.79±0.20 ml/g kidney wt/min, $p<0.001$) and 29% in group 2 (from 3.71±0.16 to 4.79±0.20 ml/g kidney wt/min, $p<0.001$). GFR increased by 34% in group 1 (from 1.06±0.05 to 1.42±0.13 ml/g kidney wt/min, $p<0.01$) and by 33% in group 2 (from 1.13±0.14 to 1.50±0.08 ml/g kidney wt/min, $p<0.01$). However, CEI had no effect on filtration fraction in either group. In group 1, the rats receiving CEI alone, there were no further changes in mean arterial blood pressure or in any of the renal hemodynamic parameters. Complete inhibition of the pressor response to angiotensin I was confirmed over the full 4 hours of experimental period.

In group 2, infusion of ANF during continuing converting enzyme inhibition (Figure 1) resulted in
an additional 23% increase in GFR (from 1.50±0.08 to 1.84±0.14 ml/g kidney wt/min, p<0.01). Renal plasma flow did not increase in parallel with GFR such that filtration fraction was significantly elevated by ANF (from 0.32±0.02 to 0.48±0.04, p<0.01). Filtration fraction remained elevated 30–90 minutes after the ANF infusion was stopped. Again there were no changes between control and experimental periods.

Table 1. Effects of Angiotensin Converting Enzyme Inhibitor and Atrial Natriuretic Factor on Mean Arterial Blood Pressure, Hematocrit, Urinary Water, and Electrolyte Excretion

<table>
<thead>
<tr>
<th>Period</th>
<th>MABP (mm Hg)</th>
<th>Hct (%)</th>
<th>V (µl/min)</th>
<th>UNV (µmol/min)</th>
<th>FENa (%)</th>
<th>UaV (µmol/min)</th>
<th>FEK (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (n=8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Control</td>
<td>113.5±2.3</td>
<td>43±0.3</td>
<td>10.83±1.10</td>
<td>0.49±0.12</td>
<td>0.14±0.03</td>
<td>1.37±0.21</td>
<td>15.06±1.99</td>
</tr>
<tr>
<td>CEI</td>
<td>92.8±2.8†</td>
<td>43±0.3</td>
<td>24.54±4.94†</td>
<td>3.67±0.79†</td>
<td>0.78±0.18†</td>
<td>1.71±0.19</td>
<td>14.31±1.35</td>
</tr>
<tr>
<td>CEI</td>
<td>90.5±2.9*</td>
<td>43±0.6</td>
<td>22.58±3.15*</td>
<td>3.89±0.69*</td>
<td>0.80±0.13*</td>
<td>1.62±0.20</td>
<td>11.82±1.04</td>
</tr>
<tr>
<td>CEI</td>
<td>92.6±3.6†</td>
<td>43±0.3</td>
<td>19.20±2.89†</td>
<td>2.94±0.49†</td>
<td>0.70±0.12†</td>
<td>1.29±0.19</td>
<td>11.06±1.17</td>
</tr>
<tr>
<td>Group 2 (n=8)</td>
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<td></td>
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</tr>
<tr>
<td>Control</td>
<td>114.6±3.3</td>
<td>43±0.2</td>
<td>10.93±1.22</td>
<td>0.53±0.19</td>
<td>0.12±0.03</td>
<td>1.58±0.09</td>
<td>15.54±1.17</td>
</tr>
<tr>
<td>CEI</td>
<td>93.8±2.8*</td>
<td>43±0.3</td>
<td>23.97±4.34†</td>
<td>3.71±1.20†</td>
<td>0.72±0.22‡</td>
<td>2.38±0.24</td>
<td>17.44±1.57</td>
</tr>
<tr>
<td>CEI+ANF</td>
<td>89.4±2.4*‡</td>
<td>44±0.4‡</td>
<td>46.84±4.96*§</td>
<td>8.24±0.96*§</td>
<td>1.35±0.16*‡</td>
<td>2.15±0.26</td>
<td>13.88±2.59</td>
</tr>
<tr>
<td>CEI</td>
<td>91.8±2.3*‡</td>
<td>44±0.2‡</td>
<td>26.71±3.53‡</td>
<td>3.36±0.53‡</td>
<td>0.78±0.12*‡</td>
<td>1.16±0.26</td>
<td>10.20±1.88</td>
</tr>
</tbody>
</table>

Urine values are averages of three 20-minute collection periods. MABP, mean arterial blood pressure; Hct, hematocrit; V, urine flow rate; UNV, sodium excretion; FENa, fractional sodium excretion; UaV, potassium excretion; FEK, fractional potassium excretion; CEI, converting enzyme inhibitor enalaprilat 5 mg/kg body wt as a single injection after the control period; CEI+ANF, atrial natriuretic factor infusion (10 ng/min) during continuing CEI infusion. FENa, FEK are shown as percent of filtered load.

Differences from control, *p<0.05, **p<0.01, ***p<0.001. Differences from previous experimental period, †p<0.05, ‡p<0.01, §p<0.001.

Figure 2. Bar graphs showing changes in proximal and distal tubular reabsorption after converting enzyme inhibition (CEI) and infusion of atrial natriuretic factor (ANF) during continuing CEI (CEI+ANF). Values are averages of three 20-minute urine collection periods. C/Li, lithium clearance; APR, absolute proximal reabsorption; FPRNa, fractional proximal reabsorption of sodium; FDRNa, fractional distal reabsorption of sodium; C control period; CEI, periods of continuing converting enzyme inhibition after the control period; CEI+ANF, period of ANF infusion during continuing CEI. Levels of significant differences between control and experimental periods are shown as *p<0.05, **p<0.01, or ***p<0.001 and between consecutive experimental periods as †p<0.05 or ‡p<0.01.
 decreased by 10% with CEI alone in group 1 (from 68.94±2.88% to 58.35±3.98%, p<0.05) and 13% in group 2 (from 71.39±2.94% to 58.09±5.30%, p<0.05). FRDNa increased with CEI alone (group 1 from 30.71±2.86% to 38.12±3.23%, p<0.05; group 2 from 27.65±2.33% to 43.57±5.48%, p<0.01). Addition of ANF (group 2) did not produce any further significant change in CLa, FPRNa, or FDRNa compared with the preceding CEI period or with the CEI-treated rats (group 1).

The changes in GFR, APR, and proximal GTB are summarized in Figure 3. With CEI only, GFR increased by 34% and 33% (groups 1 and 2, respectively), but the corresponding changes in APR were only 18% (from 0.73±0.04 to 0.86±0.05 ml/g kidney wt/min) and 16% (from 0.75±0.04 to 0.87±0.10 ml/g kidney wt/min). Thus during suppression of angiotensin production proximal GTB was only 52% and 48% effective in group 1 and group 2, respectively.

These values were significantly different (p<0.01) from 100% or "perfect" proximal GTB, which would represent parallel changes in APR and GFR.

With ANF infusion during CEI (group 2), GFR increased by a further 23% to reach 63% above control levels, and the corresponding APR increase was 16% indicating 70% effective proximal GTB. This level of operation of proximal GTB was not significantly different from that seen with CEI alone in group 1.

Discussion

The present experiments explore the proposition that atrial peptides exert their remarkable natriuretic effect by interfering with the normal actions of angiotensin on the proximal tubule. Angiotensin is an acknowledged factor augmenting sodium and water reabsorption in this segment of the nephron.42

The quantitative importance of this action is evidenced here by the severe disruption to proximal GTB caused by enalaprilat (50% effective) and by our previous finding that correction is possible with infused angiotensin II or angiotensin III.32 A similar major disruption to proximal GTB (30% effective) was also demonstrated in our previous experiments using ANF alone42 emphasizing the possibility of an ANF-angiotensin II interaction at the level of the proximal tubule. The use of lithium as the marker of proximal sodium reabsorption allows this possibility to be tested quantitatively on intact kidneys and also allows conclusions about the importance of GFR and distal nephron function in the natriuretic actions of ANF and CEI.

Our previous study8 established the actions of ANF when infused alone at a low dose and demonstrated the stability of the indexes of systemic and renal function during CEI or vehicle infusion. ANF caused slight hypotension, marked hyperfiltration, and increased filtration fraction (to 0.41). Peritubular physical forces would therefore have favored reabsorption but FPRNa fell 15%, proximal GTB was only 30% effective and UNaV rose 10-fold. By comparison, when glucagon raised GFR to the same extent there was no interference with proximal glomerulotubular balance, and UNaV increased only 2.7-fold. These considerations lead to the conclusion that disruption of proximal GTB is quantitatively the dominant factor leading to natriuresis with ANF and likely to be its most important physiological action. It is pertinent to note that while glucagon does not display any specific binding to the proximal tubule,43 ANF exhibits a low density of high affinity binding receptors30 and also putative silent clearance receptors,44 each of which might underlie a proximal action.

In the experiments reported here, in agreement with our previous report,32 CEI (enalaprilat) induced natriuresis and diuresis despite a fall in mean arterial blood pressure. In anesthetized rats, the extent of the hypotensive response to CEI is largely dependent on the activity of the renin-angiotensin system.
In a similar study, control plasma renin concentration was 439±48 ng/ml consistent with stimulation of renin release due to anesthesia and may be compared with a value of 180±20 ng/ml in tail-vein plasma from conscious rats (S.L.S., unpublished observations).

When ANF was administered during blockade of angiotensin II production (group 2), GFR rose further but renal plasma flow did not change and filtration fraction reached a surprising 0.48 persisting even after ANF was withdrawn. This effect could reflect increased glomerular ultrafiltration coefficient ($K_t$) or be due to a rise in postglomerular resistance resulting from efferent arteriolar vasostriction or increased peritubular flow resistance due to hemococoncentration. Taking into account the continuing hypotension and constant or reducing blood flow, this degree of enhanced ultrafiltration may well require a combination of all of these effects. The hyperfiltration response is clearly not related to the normal glomerular actions of angiotensin, which in these experiments appear to be directed exclusively at tone in the glomerular arteriole because CEI caused increased renal plasma flow without change in filtration fraction. Indeed, it seems likely that the failure of renal plasma flow to rise with ANF results from high efferent hematocrit and consequent increased flow resistance in the efferent arteriole. These data indicate that ANF can directly increase glomerular $K_t$ and that ANF inhibits angiotensin II on mesangial cell contractility.

When ANF was added to CEI, there was a further increase in the extent of natriuresis due solely to the rise in GFR without further effect on fractional proximal reabsorption (i.e., CEI did not block the natriuretic response to ANF but appeared to subvert the proximal component of its action). These data may be interpreted to indicate that the proximal component of inhibition of tubular reabsorption by ANF is dependent on the presence of angiotensin II. This conclusion is consistent with our previous observation that ANF inhibits angiotensin II-stimulated proximal sodium reabsorption. An alternative or perhaps complementary explanation involves predicted changes in peritubular physical factors influencing proximal fluid uptake. In group 2, ANF caused a small decrease in mean arterial blood pressure of approximately 4.5 mm Hg compared with the value during CEI alone, and filtration fraction increased to 0.48. Proximal GB was unaltered during CEI+ANF infusion (Figure 3), and it may be inferred that the rise in efferent oncotic pressure predicted from the increase in filtration fraction provided a balance of peritubular Starling forces favorable for enhanced reabsorption in response to increased filtered load. During CEI, the increase in GFR caused by ANF was associated with perfect proximal GB, albeit at the low level of fractional proximal reabsorption caused by CEI. This indicates that angiotensin is not obligatory for adjustments in proximal transport with changes in GFR but for this to be evident, filtration fraction and peritubular oncotic pressure may have to reach very high levels.

Consequent on the reduced fractional proximal sodium reabsorption with CEI, fractional distal sodium reabsorption increased but did not rise further when ANF was given during CEI. This suggests that a plateau had been reached for the load-dependent transport characteristics of the distal nephron. Relevant to this, potassium excretion did not increase with CEI or CEI+ANF, which may reflect decreasing levels of mineralocorticoids as angiotensin II disappears from the circulation during CEI. ANF alone did increase potassium output slightly, consistent with a presumed lesser inhibition of angiotensin levels.

Our results are consistent with the proposition that a major action of ANF on the kidney is through interference with the angiotensin II-stimulated component of proximal tubular reabsorption. This question remains controversial particularly since others have failed to demonstrate such an effect. The explanation for this apparently contradictory evidence may be that our previous experiments used simultaneous luminal and peritubular micropuncture techniques to examine tubular responses to angiotensin II and ANF independent of filtered load and peritubular physical factors. In contrast, Liu and Cogan administered the peptides by intravenous infusion thus incurring the additional problems of changes in renal perfusion pressure and efferent oncotic pressure due to a presumed rise in filtration fraction. These effects would be expected to enhance proximal fluid reabsorption and perhaps obscure an inhibitory effect of ANF on proximal angiotensin II-stimulated transport as discussed above. The critical factor determining proximal responsiveness to ANF may be the intrarenal angiotensin II concentration and the magnitude of net peritubular reabsorptive forces may override hormonal influences. Additional studies are required to resolve these issues. Also, although it is recognized that the renal responses to CEI are predominantly due to the effects of removal of angiotensin II, the possibility remains that kinins or prostaglandins will accumulate after inhibition of converting enzyme and may influence renal function and urinary sodium excretion. Recent studies on prostaglandin mediation of ANF have, however, shown that although the redistribution of renal blood flow away from superficial nephrons into the deep cortex is dependent on prostaglandins, neither this effect nor increased prostaglandin synthesis are important mediators of ANF-induced natriuresis.

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