Opposite Effects of Enalapril and Nitrendipine on Natriuretic Response to Atrial Natriuretic Factor

Renal Function Evaluated With Clearance Studies in Humans

Carlo A. Gaillard, Hein A. Koomans, Ton J. Rabelink, Peter Boer, and Evert J. Dorhout Mees

In clearance studies, we analyzed the effect of Ca\(^{2+}\) entry blockade with nitrendipine treatment (20 mg b.i.d. for 4 days) and of converting enzyme inhibition with enalapril treatment (20 mg b.i.d. for 4 days) on renal response to atrial natriuretic factor (ANF) (25 μg bolus followed by an infusion of 0.03 μg/kg/min for 90 minutes) in six healthy volunteers who were taking 300 mmol sodium daily. In a control study ANF was administered without Ca\(^{2+}\) entry blockade or converting enzyme inhibition. Natriuresis rose from 239±38 to 605±137 μmol/min in the control study (p<0.05), from 330±53 to 943±152 μmol/min with Ca\(^{2+}\) entry blockade (p<0.05), and from 236±22 to 344±39 μmol/min with converting enzyme inhibition (NS). ANF induced a rise in maximal free water clearance, inulin clearance, and in the excretion of multiple electrolytes except potassium. Fractional lithium reabsorption fell. In general, these effects were stronger during Ca\(^{2+}\) entry blockade and blunted during converting enzyme inhibition. p-Aminohippurate clearance tended to decrease during the control study (NS), remained constant during Ca\(^{2+}\) entry blockade, and decreased significantly when ANF was infused during converting enzyme inhibition (p<0.05 vs. control and vs. Ca\(^{2+}\) entry blockade study). Blood pressure was lowered by Ca\(^{2+}\) entry blockade and, to a somewhat greater extent, by converting enzyme inhibition, but ANF administration induced no additional fall except for a short-term drop during Ca\(^{2+}\) entry blockade. From these data we conclude that, in healthy humans, the effects of ANF on natriuresis and renal sodium handling are enhanced by Ca\(^{2+}\) entry blockade and blunted by converting enzyme inhibition. These effects might be explained by amplification of (preglomerular?) ANF-induced vasodilation during Ca\(^{2+}\) entry blockade and amplification of (postglomerular?) ANF-induced vasoconstriction during converting enzyme inhibition. (Hypertension 1989;13:173-180)

In isolated perfused rat kidneys Ca\(^{2+}\) entry blockade with verapamil was reported to inhibit the hemodynamic and natriuretic effect of atrial extract.\(^1\) By contrast, it was recently shown that nifedipine, although preventing the renal hemodynamic effect, potentiated the natriuretic effect of atrial natriuretic factor (ANF) in anesthetized rabbits.\(^2\) This study\(^2\) could not confirm inhibition of ANF-natriuresis, but it was considered that anes-...
response to ANF in the same healthy humans. Clearance experiments were performed during infusion of ANF in a control study, after 4 days of Ca\(^{2+}\) entry blockade by treatment with nitrendipine, and after 4 days of converting enzyme inhibition by treatment with enalapril. Our previous study, in which enalapril appeared to attenuate the natriuretic effect of ANF, was performed while the subjects were maintained on a low sodium diet. Consequently, there was a large drop in blood pressure, which could have interfered with the natriuretic effect of ANF. To avoid large differences in blood pressure during Ca\(^{2+}\) entry blockade and converting enzyme inhibition in the current study, a diet rich in sodium was prescribed. Nitrendipine enhanced natriuresis after ANF, whereas enalapril had an attenuating effect.

**Subjects and Methods**

Studies were carried out in six healthy male volunteers, mean age 23.2±0.8 years. Informed consent was obtained and the study was approved by the Hospital Ethical Committee for Studies in Humans. As outpatients the subjects were maintained on a diet containing 300 mmol sodium and 100 mmol potassium daily, and clearance studies (see below) were performed on the morning of the 5th, 10th, and 18th day of this diet. After the first clearance study, the dihydropyridine Ca\(^{2+}\) antagonist nitrendipine (20 mg b.i.d.) was started. The final dose was taken on the morning of the second clearance study 2 hours before the start of the study. After the second clearance study nitrendipine was discontinued and, after a 4-day washout period, enalapril (20 mg b.i.d.) was prescribed. Again, the final dose was taken 2 hours before the clearance study. The subjects visited the metabolic ward daily at noon where meals were provided and body weight was measured. Twenty-four-hour urine collections were made throughout the study.

On the eve of each clearance study 400 mg lithium carbonate was ingested at 10:00 PM. Clearance studies were carried out between 8:30 AM and 1:00 PM after an overnight fast and with the subjects in supine position. At 8:30 AM the subjects drank a water load of 20 ml/kg, and additional water matching urine output was supplied for the remainder of the clearance study. After 30 minutes a constant infusion of inulin and p-aminohippurate (PAH) into a lower arm vein was started, preceded by a priming dose. After a minimum 1.5-hour equilibration period, and when urine osmolality had reached a minimal value, three freely voided urine samples were collected at 20-minute intervals. Then a 90-minute ANF infusion (0.03 \(\mu g/\text{kg/min}\)) was started, preceded by a bolus injection of 25 \(\mu g\) ANF. During the infusion three urine collections were made. Blood samples were taken halfway through each collection period via an intravenous cannula placed on the lower arm contralateral to the infusion arm. During the clearance study, blood pressure was recorded with an automatic sphygmomanometer device (Omega 1000, Invivo Research Lab. Inc., Tulsa, Oklahoma) at regular intervals.

Urine and blood samples were analyzed for: osmolality by freezing point depression; sodium and potassium by flame photometry; chloride, phosphate, calcium, magnesium, and uric acid with a Technicon RA-autoanalyzer (Tarrytown, New York); lithium with a Perkin Elmer 3030 Atomic Absorption Spectrophotometer (Norwalk, Connecticut); insulin; and PAH. Insulin was hydrolyzed to fructose and then determined photometrically with indolacetic acid. PAH was determined photometrically by a chromogenic aldehyde reaction. Blood for determining levels of plasma renin activity (PRA), aldosterone, and ANF was taken on the day of the clearance study before and 75 minutes after the start of ANF infusion. PRA (pmol angiotensin I/1/sec) and plasma aldosterone were determined by radioimmunoassay. ANF was extracted from 2.5 ml plasma by reversed phase chromatography using Baker butylsilane wide pore extraction columns (Phillipsburg, New Jersey), followed by elution with methanol/trifluoroacetic acid 99:1 vol/vol (recovery of ANF 62%). After evaporation the extract was dissolved in radioimmunoassay buffer and aliquots were used for determination by radioimmunoassay using antibody of Peninsula Laboratories (Merseyside, UK) according to the manufacturer's instructions (coefficients of variation interassay 17%, intra-assay 11%, ED\(_{50}\) 8 fmol, lower limit of sensitivity 0.5 fmol). Values were corrected for percent recovery. Angiotensin converting enzyme activity was measured in blood obtained before the second clearance study by a colorimetric method, whereas plasma nitrendipine concentration was measured in blood obtained before the third clearance study by gas chromatography on a fused silica capillary with electron-capture detection.

The ANF used for infusion was the synthetic 28-amino acid compound (human ANF [99-126]) obtained from Bissendorf Peptide GmbH, Hanover, FRG.

**Calculations**

Mean arterial pressure was calculated as the sum of one third of the systolic pressure plus two thirds of the diastolic pressure. The clearance of inulin (C\(_{\text{in}}\)) and PAH (C\(_{\text{PAH}}\)) were regarded as markers of glomerular filtration rate (GFR) and effective renal plasma flow (ERPF), respectively. Free water clearance (C\(_{\text{H,O}}\)) during maximal diuresis was taken as an index of sodium reabsorption in the diluting segment, which is defined as the nephron beyond the point of isotonicity in the thick ascending limb of Henle's loop. The C\(_{\text{H,O}}\) plus the clearance of chloride (C\(_{\text{Cl}}\)) was regarded as an index of delivery to the diluting segment. Changes in the term ([C\(_{\text{H,O}}\)+C\(_{\text{Cl}}\)]/C\(_{\text{in}}\)) therefore represent an index of changes in the fractional solute delivery to the diluting segment, and changes in the term [C\(_{\text{H,O}}\)\(\times\)C\(_{\text{Cl}}\)]/C\(_{\text{in}}\)
TABLE 1. Baseline Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>No drug</th>
<th>Nitrendipine</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>79.1±2.5</td>
<td>78.8±2.4</td>
<td>78.0±2.2</td>
</tr>
<tr>
<td>Sodium excretion (mmol/day)</td>
<td>286±28</td>
<td>255±17</td>
<td>269±16</td>
</tr>
<tr>
<td>Potassium excretion (mmol/day)</td>
<td>72±5</td>
<td>70±8</td>
<td>71±5</td>
</tr>
<tr>
<td>Plasma sodium (mmol/l)</td>
<td>141.3±0.7</td>
<td>139.6±0.5</td>
<td>139.0±1.0</td>
</tr>
<tr>
<td>Plasma potassium (mmol/l)</td>
<td>3.8±0.1</td>
<td>3.9±0.1</td>
<td>4.2±0.2</td>
</tr>
<tr>
<td>Plasma renin activity* (fmol Ang I/l-sec)</td>
<td>158±28</td>
<td>147±22</td>
<td>1,808±432</td>
</tr>
<tr>
<td>Plasma aldosterone* (pmol/l)</td>
<td>250±34</td>
<td>180±19</td>
<td>171±16</td>
</tr>
<tr>
<td>Plasma ANF (pmol/l)</td>
<td>23.3±3.3</td>
<td>25.0±3.6</td>
<td>20.5±2.8</td>
</tr>
</tbody>
</table>

All values are mean±SEM. Ang I, angiotensin I; ANF, atrial natriuretic factor.

*Geometric mean.

(Chicago + Co) represent an index of changes in diluting segment reabsorption. The validity of these terms has been discussed by others. The fractional excretion of sodium (FENa) and FELi was calculated with standard formula.

Statistical Analysis

Values are given as mean±SEM. Statistical analysis was performed by one-way analysis of variance (ANOVA) for repeated measures. Differences in ANF-induced changes in the control study versus differences during nitrendipine or enalapril administration were analyzed by two-way ANOVA for randomized block design. The statistical significance of the differences was tested by Student's t test for paired observations (Table 1 and Figure 3) or by the least significant difference test (Tables 2 and 3, Figures 1 and 2).12

Results

Effects of Nitrendipine and Enalapril on Baseline Data

There were no significant differences in body weight and 24-hour sodium and potassium excretion before and after treatment with either nitrendipine or enalapril (Table 1). Sodium excretion (mean values of the day before the clearance studies are presented in Table 1) matched sodium intake throughout the studies. Mean arterial pressure fell from 92.5±3.2 mm Hg during the control study, to 89.3±2.9 mm Hg during nitrendipine treatment, and to 85.5±2.0 mm Hg during enalapril treatment. Nitrendipine treatment did not affect PRA, whereas aldosterone concentration was slightly depressed (NS). During treatment with enalapril, PRA increased and plasma aldosterone decreased. Adherence to the medication also was apparent from the consistently low converting enzyme activity during enalapril treatment (0.052±0.004 μmol/l/sec; normal range in plasma, 0.3–1.2 μmol/l/sec) and from consistently demonstrable plasma natriuretic levels during nitrendipine treatment (mean 3.90±1.34 ng/mL). No change in baseline plasma ANF levels was observed during treatment with nitrendipine or enalapril. After 4 days of nitrendipine no change in GFR, ERPF, or filtration fraction was observed (Table 2).

TABLE 2. Effects of Nitrendipine and Enalapril Treatment on ANF-induced Changes in Renal Hemodynamics and Sodium Handling

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Nitrendipine</th>
<th>Enalapril</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>ANF</td>
<td>Baseline</td>
<td>ANF</td>
</tr>
<tr>
<td>C_inh (ml/min)</td>
<td>132±7</td>
<td>144±6*</td>
<td>129±4</td>
<td>153±7*</td>
</tr>
<tr>
<td>C_FGF (ml/min)</td>
<td>651±90</td>
<td>619±67</td>
<td>639±65</td>
<td>638±60</td>
</tr>
<tr>
<td>Filtration fraction (%)</td>
<td>21.5±2.0</td>
<td>24.5±2.4*</td>
<td>21.0±1.9</td>
<td>24.9±2.3*</td>
</tr>
<tr>
<td>Sodium excretion (μmol/min)</td>
<td>239±38</td>
<td>605±137*</td>
<td>330±53</td>
<td>943±152*</td>
</tr>
<tr>
<td>FEK (%)</td>
<td>1.3±0.2</td>
<td>2.9±0.6*</td>
<td>1.9±0.3</td>
<td>4.4±0.6*</td>
</tr>
<tr>
<td>Urine flow (ml/min)</td>
<td>19.0±1.5</td>
<td>24.5±2.5*</td>
<td>20.9±0.6</td>
<td>29.2±2.3*</td>
</tr>
<tr>
<td>Urine osmolality (mosm/kg)</td>
<td>60±5</td>
<td>70±6*</td>
<td>62±5</td>
<td>84±5*</td>
</tr>
<tr>
<td>C_H2O+C_NO(%)</td>
<td>11.2±0.7</td>
<td>12.5±0.6*</td>
<td>12.7±0.2</td>
<td>13.1±0.4</td>
</tr>
<tr>
<td>C_H2O+C_NO+C_inh (%)</td>
<td>12.7±0.8</td>
<td>15.8±1.2*</td>
<td>14.7±0.3</td>
<td>18.0±1.0*</td>
</tr>
<tr>
<td>C_H2O+C_NO+C_inh (%)</td>
<td>88.5±1.9</td>
<td>80.1±3.0*</td>
<td>86.5±1.4</td>
<td>73.3±2.5*</td>
</tr>
<tr>
<td>FEK (%)</td>
<td>68.9±2.7</td>
<td>64.7±2.7*</td>
<td>66.1±1.9</td>
<td>62.5±1.9*</td>
</tr>
</tbody>
</table>

All values are mean±SEM. ANF, atrial natriuretic factor; a, ANF-induced changes during nitrendipine vs. no treatment; b, ANF-induced changes during enalapril vs. no treatment; c, ANF-induced changes during nitrendipine vs. during enalapril administration; C, clearance; PAH, p-aminohippurate; FENa, fractional excretion of sodium; FELi, fractional reabsorption of lithium.

*p<0.05 compared with corresponding baseline value.

†p<0.05 compared with baseline value in control study.
Baseline sodium excretion during the clearance study was increased compared with the control study, although the difference was not statistically significant. Nitrendipine increased $C_{\text{H}_2\text{O}}/C_{\text{C}_\text{O}}$, an index of distal solute delivery, and tended to decrease fractional reabsorption of lithium. Uric acid and electrolyte excretion, with the exception of sodium and magnesium, were not different during nitrendipine therapy compared with the control study (Table 3).

Enalapril caused a marked increase in renal plasma flow accompanied by a fall in filtration fraction (Table 2). The free water clearance data and fractional lithium reabsorption were unchanged. The excretion of electrolytes and uric acid also was not different during enalapril therapy compared with the control study (Table 3).

Effects of Atrial Natriuretic Factor

Figures 1 and 2 present changes in sodium and potassium excretion, blood pressure, and renal hemodynamics throughout the clearance studies. In the control study (i.e., before administration of nitrendipine or enalapril, left columns in Figures 1 and 2), ANF had no significant effect on blood pressure, potassium excretion, or ERPF, whereas natriuresis and GFR clearly increased. To further analyze the effect of ANF on renal function, the results of the three urine collections before ANF and the three portions during ANF infusion were averaged (denoted by “baseline” and “ANF” in Tables 2 and 3). ANF increased fractional sodium excretion, maximal urine flow and free water clearance, minimal urine osmolality, and decreased fractional lithium reabsorption and the term $C_{\text{H}_2\text{O}}/(C_{\text{H}_2\text{O}}+C_{\text{C}_\text{O}})$. With the exception of potassium, ANF increased the excretion of the remainder electrolytes as well.

During nitrendipine administration many effects of ANF were enhanced, such as the rise in sodium excretion (Figure 1), the rise in minimal urine osmolality and maximal urine flow, and in the excretion of remainder electrolytes and uric acid (Tables 2 and 3). The fall in the diluting segment reabsorption index, $C_{\text{H}_2\text{O}}/(C_{\text{H}_2\text{O}}+C_{\text{C}_\text{O}})$, was also stronger than before nitrendipine. Blood pressure tended to fall shortly after the start of ANF infusion, but then rapidly returned to the preinfusion level (Figure 1). The rise in GFR tended to be larger, the difference with the control study becoming significant ($p<0.05$) in the final collection period (Figure 2). The tendency for a decrease in ERPF was absent during nitrendipine (Figure 2).

Enalapril, by contrast, attenuated or abolished most effects of ANF. This includes the rise in mean arterial pressure and sodium and potassium excretion in the control study and during nitrendipine or enalapril treatment. Values are mean±SEM. Single ($p<0.05$) and double asterisks ($p<0.01$) indicate a significant difference from preinfusion values.
natriuretic factor infusion on inulin and p-aminohippurate (PAH) clearance in the control study and during nitrendipine or enalapril treatment. Values are mean±SEM. Single (p<0.05) and double asterisks (p<0.01) indicate a significant difference from preinfusion values.

sodium excretion and fractional lithium reabsorption as well as the data derived from maximal free water clearance. The excretion of chloride, calcium, and magnesium were also less when ANF was infused during enalapril. As in the control study, blood pressure showed no consistent fall, but ERPF decreased significantly.

Although a tendency for a decrease in PRA and plasma aldosterone could be recognized during each ANF-infusion study, only the fall in PRA when ANF was infused during enalapril administration reached significance (Figure 3). The concentration of ANF reached similar levels during the three studies.

Discussion

Our main goal was to find out whether the effect of Ca²⁺ entry blockade that was obtained by administering nitrendipine for 4 days and the effect of converting enzyme inhibition that was obtained by a similar period of administration of enalapril on the renal response to ANF would be comparable, at least directionally. Obviously this was not the case, since Ca²⁺ entry blockade amplified and converting enzyme inhibition attenuated the response to ANF.

In acute experiments Ca²⁺ entry blockade caused a preferential afferent arteriolar dilatation, accompanied by a rise in GFR and renal blood flow. In normotensive humans, these changes are probably modest and disappear during sustained treatment. After 4 days of nitrendipine therapy, we found no change from control in renal hemodynamics or in sodium excretion. Although a moderately negative sodium balance is commonly found during Ca²⁺ entry blockade, there was no change in body weight either. There was, however, a tendency to increased sodium excretion rate in the clearance study before ANF infusion (Table 2), probably reflecting an acute effect of the last dose of nitrendipine. The attendant increase in \( \left( C_{H_2O} + C_{Cl} \right) / GFR \) and tendency for a lower fractional reabsorp-
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...tion of lithium, both also found by others,20–22 indicate decreased reabsorption before the point of isotonicity in the medullary thick ascending limb of Henlé’s loop.

When infused in this situation, ANF not only induced more diuresis and natriuresis than before Ca2+ entry blockade, but also induced a larger rise in GFR, minimal urine osmolality, free water clearance, and uric acid, phosphate, Ca2+, and magnesium excretion. The fractional lithium reabsorption decreased to the same extent as in the control study. These effects of ANF were the same as those found in previous studies5,23,24 and, although there are many uncertainties inherent in these methods, suggest that the natriuresis caused by ANF involved a rise in filtered load and a fall in fractional reabsorption rates in both proximal and distal nephron segments. Apparently, these phenomena tend to be enhanced when ANF is given during Ca2+ entry blockade.

The mechanism of this amplification could be explained from what is known of intracellular events. Evidence exists that reduction of target cell cytosolic free Ca2+ is an important step by which ANF establishes its effects.25 The mechanism involved is as yet unclear: ANF may either impair cellular Ca2+ entry, accelerate its extrusion, or impair its release from intracellular stores.26–29 A decrease of cellular free Ca2+ after ANF has been found in vascular smooth muscle and mesangial cells28–30 and could be essential for the relaxation of these cells. Although it is not known how such effects within the kidney are related to the natriuretic effect of ANF, it is conceivable that the ability to restore intracellular Ca2+ (e.g., by entry through adrenergic or angiotensin II–activated Ca2+ channels31,32) would act in the opposite direction and thus determine the ultimate natriuresis of ANF. Thus, by impairing this intracellular Ca2+ movement, Ca2+ entry blockade could amplify the action of ANF.

ANF raises GFR by afferent arteriolar and mesangial relaxation33–35 and also inhibits normal tubuloglomerular feedback.36 Normal tubuloglomerular feedback seems to depend on intracellular Ca2+ at the (macula densa) receptor level as well as the (afferent arteriolar and mesangial cell) effector level,14 which could explain the enhanced rise in GFR after ANF during Ca2+ entry blockade. The fall in fractional sodium reabsorption in proximal as well as distal nephron segments after ANF is probably due to a vasodilation-induced rise in peritubular hydrostatic pressure and flow,37–39 which could also be stronger during Ca2+ entry blockade. Whether the direct suppressive effect of ANF on reabsorption in the medullary and final collecting duct, as documented in micropuncture studies,40,41 is also stronger during Ca2+ entry blockade is uncertain. Our observation of a larger rise in minimal urine osmolality during Ca2+ entry blockade would agree with such an effect. Evidence that Ca2+ entry blockade inhibits sodium reabsorption in the collecting duct is, to our knowledge, limited to one micropuncture study in rats showing that felodipine decreased reabsorption between late distal tubule and final urine.42

Also, when ANF was given during Ca2+ entry blockade with nifedipine, no rise in ERPF was found. However, the tendency for a fall in ERPF after ANF that occurred in the control study was absent during Ca2+ entry blockade (Figure 2). Except for a dip in blood pressure early after infusion of ANF during Ca2+ entry blockade, an exaggerated fall in blood pressure was not found throughout the present experiment (Figure 1). Enhanced extrarenal vasodilation, such as found during acute simultaneous administration of the Ca2+ entry blocker nifedipine and ANF in anesthetized rabbits,2 was not confirmed. However, we did confirm that study’s finding that Ca2+ entry blockade enhances the natriuresis of ANF. We cannot explain why inhibition of atrial extract–induced natriuresis was found in isolated perfused kidneys during Ca2+ entry blockade with verapamil,1 but the situation in vivo clearly differs in many ways from that in vitro.

Enalapril blunted the effects of ANF on natriuresis as well as on GFR. Remarkably, the magnitude of this attenuation was comparable with that seen in our previous study, where the subjects consumed only 100 mmol sodium daily.5 Apparently, a 300 mmol sodium diet, as supplied in the present study, does not suppress the renal renin-angiotensin system to the extent of eliminating the effects of converting enzyme inhibition on the kidney. The data on lithium, free water clearance, and excretion of other electrolytes are compatible with less suppression by ANF of (fractional) tubular solute reabsorption at proximal and distal nephron segments during converting enzyme inhibition than before converting enzyme inhibition. All changes in renal function seen after ANF administration were attenuated during enalapril, with the exception of the rise in filtration fraction. Converting enzyme inhibition increased ERPF, thus reflecting efferent, and perhaps afferent, vasodilation.43 The rise in filtration fraction after ANF was not predominantly due to a fall in ERPF, suggesting an exaggerated vasoconstrictive response.

Although it is difficult to explain the discrepant effects of Ca2+ entry blockade and converting enzyme inhibition on natriuresis, the changes in renal hemodynamics may present a clue. ANF has a dual effect on renal vascular tone; it is dilatory in preglomerular and constrictive in postglomerular vessels.33,34 Although documentation of the latter is inconsistent in direct studies,35 in clearance studies such as the present one ERPF often falls or tends to fall while GFR rises.24,44 Whereas preglomerular vasodilation promotes natriuresis by increasing GFR and peritubular hydrostatic pressure and flow, the postglomerular vasoconstriction might oppose natriuresis by decreasing peritubular pressure and flow. Ca2+ entry blockade could have specifically pro-
moted the dilatory effect of ANF, which is in agreement with data that indicate a preferential afferent arteriolar action of Ca\(^{2+}\) entry blockers.\(^{3,14}\) Our clearance data suggest that converting enzyme inhibition decreased the vasodilatory response, without disturbing or even amplifying the vasoconstrictive response. This reasoning is, of course, speculative, since there is still the unanswered question of how inhibition of angiotensin II formation would oppose dilatation or increase constrictive actions of ANF.

Treatment with enalapril caused a somewhat greater decrease in blood pressure than treatment with nitrendipine (Figure 1), an effect we attempted to avoid by supplying a sodium-rich diet. Since renal perfusion pressure appears to have a positive influence on natriuresis after ANF,\(^{45,46}\) it is still possible that the blunted natriuretic effect found during converting enzyme inhibition was related to the lower blood pressure. However, this cannot explain the enhanced natriuresis during Ca\(^{2+}\) entry blockade.

Although Ca\(^{2+}\) entry blockade is frequently followed by a modestly negative sodium balance, a rise in plasma aldosterone is usually absent.\(^{16,17}\) In fact, the direct influence of Ca\(^{2+}\) entry blockade may be a fall in plasma aldosterone, since angiotensin-induced aldosterone release is inhibited.\(^{47}\) Because ANF also decreases aldosterone by a direct action on the zona glomerulosa,\(^{48}\) potentiation of this effect during Ca\(^{2+}\) entry blockade is conceivable, but was not observed in the current study. However, the 75-minute observation period may have been too short to exclude such an influence.

Relative to earlier studies, the dosage of ANF used in the present study was modest. Nonetheless, the plasma concentrations measured were high, and thus may be considered unphysiological. To judge the relevance of our data for normal physiology, studies with lower infusion dosages must be undertaken. Results of such studies probably will not be basically different, since we also found that enalapril blunted the natriuresis of a 3-hour infusion of 0.01 \(\mu g/kg/min\) ANF in healthy individuals (unpublished observation).

We found in humans that the Ca\(^{2+}\) entry blocker nitrendipine enhanced the rise in GFR and natriuresis after ANF. This can be understood, since one of the intermediate steps by which ANF achieves its effects is lowering of target-cell free Ca\(^{2+}\). Our observation contrasts with the early report in isolated kidneys that verapamil decreased natriuresis by atrial extract. Enalapril, however, reduced the natriuretic effect of ANF, possibly by decreasing the vasodilatory and increasing the vasoconstrictive effect of ANF. How this effect is established remains to be elucidated.

Acknowledgments

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**KEY WORDS** • atrial natriuretic factor • converting enzyme inhibition • Ca2+ entry blockade • renal function • lithium • nitrendipine • enalapril
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