Rapid Nongenomic Effects of Aldosterone on the Renal Vasculature in Humans

Bernhard M.W. Schmidt, Ulla Sammer, Ingrid Fleischmann, Markus Schlaich, Christian Delles, Roland E. Schmieder

Abstract—There is increasing evidence for the importance of rapid nongenomic effects of aldosterone on the human vasculature. In vitro animal experiments in renal arterioles also suggest the presence of such effects on the renal vasculature. We conducted a clinical study to explore these effects in vivo in humans. Thirteen healthy male volunteers were examined. Aldosterone (500 μg) or placebo was injected intravenously with or without coinfusion of N(G) monomethyl-L-arginine (L-NMMA) in a randomized, double-blinded 4-fold crossover design. Renal plasma flow and glomerular filtration rate were measured by constant infusion clearance technique using inulin and para-aminohippuric acid. Injection of aldosterone without concomitant infusion of L-NMMA changed the renal plasma flow and glomerular filtration rate, not statistically significant compared with placebo. Coinfusion of L-NMMA unmasked the effect of aldosterone: aldosterone with L-NMMA decreased the glomerular filtration rate slightly (−1.4±6.2 mL/min), whereas infusion of L-NMMA alone increased the glomerular filtration rate (8.3±9.8 mL/min; P=0.004). L-NMMA alone decreased renal plasma flow by 58.2±7.5 mL/min, and aldosterone with L-NMMA decreased renal plasma flow by 190.0±213.7 mL/min (P=0.074). Accordingly, aldosterone with L-NMMA increased renal vascular resistance much more than L-NMMA alone (1588±237 versus 614±240 dyn×s×cm−5; P=0.014). These data indicate that aldosterone acts via rapid nongenomic effects in vivo in humans at the renal vasculature. Antagonizing the endothelial NO synthase unmasks these effects. Therefore, rapid nongenomic aldosterone effects increase renal vascular resistance and thereby mediate arterial hypertension if endothelial dysfunction is present. (Hypertension. 2006;47:650-655.)

Key Words: aldosterone ■ nitric oxide ■ glomerular filtration rate

The impact of aldosterone in cardiovascular and renal disease has recently gained new interest. Increased aldosterone production seems to be a far more common cause of arterial hypertension than believed previously, accounting for ≥10% in unselected patients.1,17 Aldosterone has been linked to myoccardial fibrosis and progression of renal disease independent of its hypertensive effects (reviewed in References 2,3). Rapid nongenomic aldosterone effects have been proposed to be of importance in human essential hypertension beyond the classical genomic aldosterone effects.4 Rapid nongenomic aldosterone effects are characterized by their rapid onset of action (within minutes) and an insensitivity to inhibitors of transcription (eg, actinomycin D) and of protein synthesis (eg, cycloheximide; reviewed in References 5,6). Rapid, nongenomic effects to the vasculature have been shown in humans by measurement of systemic vascular resistance5–10 and forearm blood flow.11,12

To date, no data looking specifically at the renal vasculature in humans are available. However, nongenomic aldosterone effects on the renal vasculature have been shown in vitro. Arima et al13 found a vasoconstriction in afferent and efferent renal arterioles by examining isolated perfused afferent and efferent arterioles from rabbit kidneys. In another study, the same group found that endothelium-derived NO modulates the vasoconstrictor response to aldosterone in rabbit pregglomerular afferent arterioles. Disrupting the endothelium, as well as blockade of endothelial NO synthase (eNOS), augmented aldosterone-induced vasoconstriction in this study.14 Uhrenholt et al15 found no effect of aldosterone alone on afferent arterioles but a suppression of depolarization induced vasoconstriction. After blockade of eNOS, the aldosterone effect was completely suppressed. Using preparation from the rat aorta, Liu et al16 showed that aldosterone in endothelium-intact vascular rings counteracted phenylephrine-induced vasoconstriction, whereas aldosterone in endothelium-denuded vascular rings enhanced phenylephrine-induced vasoconstriction. The existence of a vasoconstrictive effect of aldosterone in the renal vasculature is of importance, because renal vasoconstriction represents an important hemodynamic hallmark in the pathophysiology of arterial hypertension.17 We conducted this clinical study to assess the impact of rapid nongenomic aldosterone effects on the renal vasculature in vivo in humans.
Methods

Study Volunteers
Fifteen healthy male volunteers were enrolled in the study. All of the volunteers were subjected to a medical examination within 2 weeks before inclusion into the study. The examination consisted of medical history, physical examination, 12-lead ECG, and determination of clinical laboratory parameters. All of the subjects gave their written informed consent to participate in the study. Two volunteers had to be removed from the study without having finished >1 study period: one volunteer because of a mild allergic reaction to inulin or para-aminohippurate (PAH), the other because of nonadherence to the study schedule.

Study Design
The study was designed as a randomized, placebo-controlled, double-blinded 4-fold crossover trial. It was conducted in accordance with the guidelines for Good Clinical Practice and the declaration of Helsinki after approval by the Institutional Review Board of the Friedrich-Alexander University Erlangen-Nuremberg.

Thirteen volunteers received aldosterone or placebo together with Nω-monomethyl-L-arginine (L-NMMA) or placebo in random order in a double-blind fashion on 4 different days ≥1 week apart according to the 4-fold crossover design.18 This assures that each volunteer serves as its own control having received all 4 of the treatment combinations (placebo/placebo, placebo/aldosterone, L-NMMA/placebo, and L-NMMA/aldosterone). Study procedures were finished within 30 minutes after aldosterone bolus injection to assure rapid, presumably nongenomic origin of the observed effects.

Assessment of Renal and Systemic Hemodynamics
Renal hemodynamic parameters were determined by a constant infusion input clearance technique with inulin (InTest, Fresenius) and PAH (Clinalfa) for glomerular filtration rate (GFR) and renal plasma flow (RPF), respectively. These procedures have been described previously.19 Briefly, the examination was performed in a quiet laboratory from 8:00 AM to 12:00 AM with the subject in the supine position. The participants fasted overnight and drank 15 mL/kg of mineral water during the examination in addition to infusion of 500 mL of normal saline. After bolus infusion of inulin and PAH over 15 minutes and a subsequent constant infusion over 105 minutes, a steady state between input and renal excretion of the tracer substances was reached,19 and the administration of experimental substances was started. Glomerular hydrostatic pressure (PGlo) and resistances of the afferent and efferent glomerular artery were determined according to the model established by Gomez,20 which has been discussed in detail recently.21,22 Systemic hemodynamic parameters (ie, heart rate, stroke volume, cardiac output, blood pressure, and total peripheral resistance) were monitored by the Task Force Monitor device (CNSystems) at baseline and during the infusion.

Experimental Protocols
After 120 minutes, either aldosterone (prepared as mixed micelles, Clinalfa, 0.5 mg) or placebo (mixed micelles only, Clinalfa) were injected intravenously. At the same time, an infusion of either L-NMMA (Clinalfa; 3 mg/kg as a bolus over 5 minutes followed by infusion at a rate of 3 mg/kg per hour over the remaining 25 minutes, ie, a total dose of 4.25 mg/kg) or placebo (0.9% NaCl over 30 minutes) was started. Blood samples to determine inulin and PAH concentration were drawn at 0, 120, and 150 minutes. Each blood sample was measured in duplicate with a coefficient of variation of <5%. Aldosterone was measured by a commercially available test kit (Aldosterone MAIA, BioChem ImmunoSystems). The limit of detection of this assay is 6.0 pg/mL. Interassay variance is 6.4%, and intraassay variance is 5.4%.

Statistical Analysis
All of the statistical analyses were performed using SPSS software package (SPSS for Windows 12.0, SPSS Inc). For statistical inference, the change from baseline was calculated for each variable. Paired Student’s t test was performed to compare the effects of aldosterone versus placebo under the conditions “L-NMMA coinfusion” and “placebo coinfusion.” Primary end points of the study were the differences in GFR and RPF between aldosterone and placebo under the conditions L-NMMA coinfusion and placebo coinfusion. For these 4 comparisons, the level of significance was set to P<0.0125 (2-tailed). The other parameters were considered secondary end points, and their evaluation was exploratory with the level of significance set to P<0.05 (2-tailed). All of the values are given as mean±SE.

Results

General Characteristics
All of the volunteers were healthy according to standard laboratory parameters, physical examination including resting blood pressure, and ECG. Their mean age was 26.1±2.6 years, their height was 181.7±2.6 cm, and their weight was 77.0±2.9 kg. Resting blood pressure was 122.7±1.3 mm Hg systolic and 77.0±1.1 mm Hg diastolic at a heart rate of...

### TABLE 1. Baseline Values for Renal Hemodynamics and Differences in Renal Vascular Resistances and Glomerular Pressure From Baseline

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Aldosterone</th>
<th>Placebo</th>
<th>Aldosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPF, mL/min</td>
<td>724±44</td>
<td>661±36</td>
<td>686±43</td>
<td>765±71</td>
</tr>
<tr>
<td>GFR, mL/min</td>
<td>134±5</td>
<td>127±5</td>
<td>129±4</td>
<td>133±4</td>
</tr>
<tr>
<td>FF, %</td>
<td>19±1</td>
<td>20±1</td>
<td>19±1</td>
<td>18±1</td>
</tr>
<tr>
<td>RVR, dyn×s×cm⁻³</td>
<td>5215±402</td>
<td>5874±394</td>
<td>5761±448</td>
<td>5173±345</td>
</tr>
<tr>
<td>R₀, dyn×s×cm⁻³</td>
<td>1487±170</td>
<td>1866±243</td>
<td>1808±194</td>
<td>1592±145</td>
</tr>
<tr>
<td>Pₐ₀, mm Hg</td>
<td>66±1</td>
<td>66±1</td>
<td>65±1</td>
<td>66±1</td>
</tr>
<tr>
<td>ΔP₀, dyn×s×cm⁻³</td>
<td>11.5±77.8</td>
<td>−99.0±134.8</td>
<td>158.4±79.5</td>
<td>541.8±121.4*</td>
</tr>
<tr>
<td>ΔR₀, dyn×s×cm⁻³</td>
<td>59.2±88.4</td>
<td>41.4±56.8</td>
<td>343.2±88.2</td>
<td>610.1±78.6*</td>
</tr>
</tbody>
</table>

FF indicates filtration fraction; RVR, renal vascular resistance; R₀, resistance of afferent arterioles; Δ, difference.

*P<0.05 compared to L-NMMA/placebo.
63.2±1.7 bpm. Sodium and potassium levels were within the normal range (141.2±0.3 mmol/L and 3.93±0.03 mmol/L, respectively). The baseline values of renal hemodynamics are shown in Table 1.

**Effect of Aldosterone Injection**
Injection of aldosterone without concomitant infusion of l-NMMA increased RPF and GFR slightly compared with placebo injection. This difference was not statistically significant (Figures 1 and 2). The same holds true for the calculated $P_{\text{Glo}}$, resistances of the afferent and efferent glomerular artery estimates of glomerular pressure, and resistance of the afferent and efferent arterioles (Table 1).

**Effect of Aldosterone Injection With Concomitant l-NMMA Infusion**
Coinfusion of l-NMMA changed the effect of aldosterone on renal hemodynamics. Infusion of l-NMMA alone decreased RPF by 58.2±27.1 mL/min ($P=0.053$ for change from baseline) and aldosterone in coinfusion with l-NMMA decreased RPF by 190.0±59.3 mL/min ($P=0.008$, for change from baseline, $P=0.074$ for comparison with l-NMMA alone; Figure 1).

Infusion of l-NMMA alone increased GFR (8.3±2.7 mL/min; $P=0.01$ for change from baseline), whereas aldosterone coinfusion with l-NMMA hindered the increase in GFR ($-1.4±1.7$ mL/min; $P=0.432$ for change from baseline; $P=0.004$, for comparison with l-NMMA alone; Figure 2). Accordingly, the filtration fraction was more strongly increased by aldosterone and l-NMMA than with l-NMMA alone (4.9±0.6; $P<0.001$ for comparison with baseline versus 2.8±0.7; $P=0.001$ for comparison with baseline; $P=0.024$ for comparison of periods; Figure 3).

Aldosterone coinfused with l-NMMA strongly increased renal vascular resistance (RVR). The increase by 1588.4±237.2 dyn·s·cm⁻⁵ ($P=0.001$, for comparison with baseline) was on top of the smaller increase that was induced by l-NMMA infusion (614.0±239.8 dyn·s·cm⁻⁵; $P=0.025$ for comparison with baseline). The difference was statistically significant ($P=0.014$; Figure 4).

Infusion of l-NMMA resulted in an increase of $P_{\text{Glo}}$ (2.138±0.601 mm Hg; $P=0.004$ for the comparison with baseline) that was blunted by injection of aldosterone (0.438±0.468 mm Hg; $P=0.368$). This difference was statistically significant ($P=0.036$; Table 1). With l-NMMA, the
increase in resistance was overall smaller but showed a tendency to be more pronounced at the efferent arteriole (158.4 ± 79.5 dyn × cm⁻² for the afferent versus 343.2 ± 88.2 dyn × cm⁻² for the efferent arteriole; \( P = 0.058 \)). This was not the case with the vasoconstriction induced by l-NMMA plus aldosterone (610.1 ± 78.6 dyn × cm⁻² for the afferent versus 541.8 ± 121.4 dyn × cm⁻² for the efferent arteriole; \( P = 0.475 \); Table 1).

**Aldosterone Levels**

Aldosterone levels at baseline were 293 ± 14 pmol/L. With placebo injection, aldosterone levels remained stable at 283 ± 19 pmol/L after 15 and 280 ± 17 pmol/L after 30 minutes. Aldosterone injection increased the levels to 29160 ± 2989 pmol/L after 15 and 17307 ± 989 pmol/L after 30 minutes.

**Systemic Hemodynamics**

Systemic hemodynamics at baseline and during infusion are shown in Table 2. No statistically significant changes occurred.

**Discussion**

We have demonstrated for the first time rapid, nongenomic effects of aldosterone on the renal vasculature in humans. If given alone, aldosterone had no significant vasoconstrictive effect, but with infusion of l-NMMA, aldosterone emerged as a potent renal vasconstrictor. Additional analysis showed that the observed vasoconstriction is more pronounced at the afferent arteriole than at the efferent arteriole. The nongenomic nature of these aldosterone effects is likely because of the short time frame of measurement. RPF and GFR were measured at baseline and within 30 minutes thereafter. Thus, genomic effects appeared most unlikely to mediate the observed vasoconstrictive action of aldosterone on renal vessels, because they require more time to act on target organs. Considering that changes in renal perfusion need some time to lead to measurable changes of serum concentrations of PAH and inulin, the observed effects might have been initiated 10 to 15 minutes after bolus injection at the latest.²³

Rapid, nongenomic effects of aldosterone on isolated afferent and efferent arterioles from rabbit kidneys have been examined recently by Arima et al.¹³ They showed a vasoconstrictor effect of aldosterone that occurred at 10⁻⁴ M aldosterone in the efferent and at 5 × 10⁻⁴ M in the afferent arteriole. Despite the higher sensitivity of the efferent arterioles for aldosterone, the effects seen at higher concentrations of aldosterone were identical. The magnitude of the effect was in the range of 15% to 30% reduction of luminal diameter. A decrease in the luminal diameter of this magnitude translates into a doubling of RVR, because vascular resistance is reciprocal to the fourth power of vascular radius. Thus, these rather small changes, compared with other vasoconstrictors, such as angiotensin II, can cause relevant increases in vascular resistance. However, the effect on RVR had not been measured in experimental animals or humans.

The vasoconstrictive effects of aldosterone seen in the study by Arima et al.¹³ were clearly nongenomic. The authors have shown this by classical blocking experiments with actinomycin D, cycloheximide, and spironolactone, of which neither compound blocked the effect of aldosterone. In addition, these effects were sustained using albumin-conjugated aldosterone, which is unable to enter the cytoplasm and activate the mineralocorticoid receptor. In a second study, the same group examined the importance of the endothelium for the modulation of these effects and found that both endothelial denudation and pharmacological blockade of eNOS increased the sensitivity of the efferent arterioles to aldosterone and increased the vasoconstrictive effect of aldosterone.¹⁴

In contrast, Uhrenholt et al.¹⁵ showed that aldosterone has no effect on the diameter of isolated afferent rabbit arterioles. They found that aldosterone abolishes depolarization-mediated con-

### Table 2. Systemic Hemodynamic Parameters at Baseline and Differences From Baseline During Infusion of Aldosterone/Placebo and l-NMMA/Placebo

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Aldosterone</th>
<th>Placebo</th>
<th>Aldosterone</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, bpm</td>
<td>53.5 ± 2.2</td>
<td>54.9 ± 2.2</td>
<td>0.204</td>
<td>58.5 ± 3.9</td>
<td>54.1 ± 1.5</td>
</tr>
<tr>
<td>SV, mL</td>
<td>90.5 ± 8.0</td>
<td>90.8 ± 7.5</td>
<td>0.936</td>
<td>91.9 ± 7.0</td>
<td>90.3 ± 7.0</td>
</tr>
<tr>
<td>C0, L/min</td>
<td>4.7 ± 0.3</td>
<td>4.9 ± 0.3</td>
<td>0.535</td>
<td>5.2 ± 0.3</td>
<td>4.8 ± 0.3</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>119.3 ± 2.0</td>
<td>118.2 ± 2.2</td>
<td>0.549</td>
<td>118.2 ± 1.6</td>
<td>119.4 ± 2.5</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>75.5 ± 2.3</td>
<td>76.0 ± 1.9</td>
<td>0.772</td>
<td>74.3 ± 2.1</td>
<td>74.8 ± 2.4</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>89.7 ± 2.0</td>
<td>89.2 ± 1.9</td>
<td>0.788</td>
<td>87.3 ± 1.9</td>
<td>88.5 ± 2.3</td>
</tr>
<tr>
<td>TPR, mm Hg × min × L⁻¹</td>
<td>20.2 ± 1.8</td>
<td>19.2 ± 1.2</td>
<td>0.263</td>
<td>17.6 ± 1.4</td>
<td>19.3 ± 1.6</td>
</tr>
<tr>
<td>( \Delta ) HR, bpm</td>
<td>1.6 ± 0.5</td>
<td>1.9 ± 1.2</td>
<td>0.689</td>
<td>−8.4 ± 4.7</td>
<td>−4.3 ± 0.7</td>
</tr>
<tr>
<td>( \Delta ) SV, mL</td>
<td>−6.6 ± 1.8</td>
<td>−6.2 ± 2.3</td>
<td>0.777</td>
<td>−8.3 ± 5.1</td>
<td>−11.3 ± 2.7</td>
</tr>
<tr>
<td>( \Delta ) CO, L/min</td>
<td>−0.2 ± 0.1</td>
<td>−0.2 ± 0.1</td>
<td>0.774</td>
<td>−1.1 ± 0.2</td>
<td>−0.9 ± 0.1</td>
</tr>
<tr>
<td>( \Delta ) SBP, mm Hg</td>
<td>−0.3 ± 0.8</td>
<td>0.1 ± 0.7</td>
<td>0.699</td>
<td>3.7 ± 1.6</td>
<td>0.2 ± 0.6</td>
</tr>
<tr>
<td>( \Delta ) DBP, mm Hg</td>
<td>−0.5 ± 0.8</td>
<td>−0.1 ± 0.6</td>
<td>0.547</td>
<td>3.0 ± 1.5</td>
<td>2.1 ± 0.7</td>
</tr>
<tr>
<td>( \Delta ) MAP, mm Hg</td>
<td>−0.6 ± 2.0</td>
<td>0.1 ± 0.7</td>
<td>0.429</td>
<td>3.4 ± 1.6</td>
<td>1.2 ± 0.8</td>
</tr>
<tr>
<td>( \Delta ) TPR, mm Hg × min × L⁻¹</td>
<td>0.8 ± 0.6</td>
<td>0.7 ± 0.6</td>
<td>0.934</td>
<td>5.5 ± 0.6</td>
<td>5.0 ± 0.6</td>
</tr>
</tbody>
</table>

HR indicates heart rate; SV, stroke volume; CO, cardiac output; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; TPR, total peripheral vascular resistance; \( \Delta \), difference.
striction by a rapid mineralocorticoid receptor and phosphatidylinositol 3-kinase–dependent mechanism. These different results are difficult to reconcile at present. However, Uhrenholt et al, in concordance with Arima et al, showed that in their experimental model the vasodilative aldosterone effect was abolished after blockade of eNOS. These results are in agreement with the data by Liu et al and our data from the human forearm. Liu et al showed that aldosterone in intact aortic rings from rats hinders phenylephrine-induced vasoconstriction, but in endothelium-denuded rings it enhances phenylephrine-induced vasoconstriction. In our human study, a small vasodilatation occurred if aldosterone was given alone. However, L-NMMA with intraarterial infusion of aldosterone caused an exaggerated vasoconstriction suggesting an increased eNOS activity at baseline that, in turn, was induced by aldosterone. On the other hand, with regard to interventions directed to vascular smooth muscle cells, aldosterone may lead to vasoconstriction: aldosterone by rapid nongenomic effects enhanced phenylephrine induced vasoconstriction and reduced NO-mediated vasodilatation.

A rapid, nongenomic action on endothelial cells has been shown earlier by Schneider et al. They found that aldosterone increases free intracellular calcium as determined by fura 2 fluorometry in single porcine endothelial cells. Because an increase in intracellular calcium in endothelial cells causes increased production of NO, these data might reflect the cellular basis of the rapid, nongenomic effects of aldosterone on endothelial function.

The method of exploring endothelial function in the renal vascular bed has been validated by our group before. The effect of L-NMMA in normotensive, healthy young volunteers on RPF and GFR is a decrease of RPF and an increase of GFR. The results from this study are quite identical with what we have seen before in young individuals. With regard to the L-NMMA infusion, we observe some patients in whom we cannot find any cardiovascular effect with the dose used here. This means that we, indeed, induce a state of eNOS dysfunction that reflects the endothelial dysfunction found in cardiovascular disease.

It has been shown that aldosterone causes systemic vasoconstriction in patients with suspected coronary artery disease and in healthy male volunteers. This effect is not found in the study presented here and in another study also conducted in healthy male volunteers. The most likely reason for this is the limited power of our study to detect a possible increase in total peripheral resistance.

Our present results are mainly in line with the results from the animal experiments. We did not find a statistically significant effect of aldosterone alone on renal vasculature compared with placebo. Indeed, there was a trend, if any, toward a slight vasodilation caused by aldosterone. Our data, therefore, support the hypothesis that rapid nongenomic aldosterone effects are not detrimental as long as endothelial function is intact. Conversely, if endothelial function is impaired, indicated by reduced eNOS activity, aldosterone causes vasoconstriction of renal blood vessels. In the study by Arima et al, the effect was similar in the afferent and the efferent arteriole. Our calculations using the formulas by Gomez suggest only a slightly stronger vasoconstriction of the afferent than the efferent arteriole in humans that, however, translates into a decrease of glomerular pressure compared with L-NMMA infusion.

There are some limitations of our study. First, RVR was only a secondary predefined end point of our study, because we chose only to use primary measured parameters (GFR and RPF) as primary end points. Therefore, one can argue that, in the strict sense, we only showed a statistically significant effect of aldosterone versus placebo on GFR during L-NMMA infusion. The conclusion that aldosterone causes renal vasoconstriction is not based on a statistically significant decrease in RPF (P = 0.074) but on a significant change in RVR, which is calculated from RPF and mean arterial pressure. Second, we used solely the short time frame to assure the nongenomic nature of the effects. We, therefore, cannot totally exclude genomic effects. In a clinical study, it is not possible to use inhibitors of translation or transcription because of the toxicity of these compounds. Third, the aldosterone plasma concentrations reached are supraphysiologic but are still far lower than concentrations expected to induce unspecific membrane effects (≥10 μmol/L). The aldosterone levels seen in our study are found in patients with severe secondary aldosteronism. Furthermore, there is an ongoing discussion on the local production of aldosterone in the heart, in blood vessels, and in the kidney. Thus, tissue levels, rather than aldosterone plasma levels, might be important when assessing cardiovascular aldosterone actions. Therefore, the high plasma levels observed in this study, in addition to being found in rare cases of secondary aldosteronism, may actually be representative of pathophysiological or even physiological tissue levels. However, additional studies in vitro are required to confirm the concept of local production of aldosterone in blood vessels and to estimate the “real” aldosterone levels acting on the vessel wall in the kidney.

To additionally elucidate the precise mechanisms that cause vasoconstriction in the renal vasculature, for example, by using different blocking agents of the mineralocorticoid receptor, was beyond the scope of this study. Introducing a blocking agent would not have lead to conclusive results, because recent experimental data on different aldosterone antagonists with regard to blocking nongenomic effects are conflicting.

Perspectives

Aldosterone clearly has detrimental effects on the progression of chronic kidney disease, but the relative importance of rapid nongenomic aldosterone effects with this regard remains to be determined. To additionally elucidate the clinical importance of rapid, nongenomic aldosterone effects to the renal vasculature, more preclinical data are necessary that characterize antagonists of these effects. The proof of these effects in humans, as provided by this study, should motivate such additional research. Similarly, with regard to potential therapeutic approaches, more studies in vivo are needed. This is of explicit importance, because from some in vitro studies there is evidence that the new mineralocorticoid receptor antagonist eplerenone might block nongenomic effects that are not blocked by spironolactone.

Acknowledgments

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References

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