Angiotensin receptor blockers shift the circadian rhythm of blood pressure by suppressing tubular sodium reabsorption

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Angiotensin II receptor blocker (ARB) restored the circadian rhythm of the blood pressure (BP) from a nondipper to a dipper pattern, similar to that achieved with sodium intake restriction and diuretics (Fukuda M, Yamanaka T, Mizuno M, Motokawa M, Shirasawa Y, Miyagi S, Nishio T, Yoshida A, Kimura G. J Hypertens 26: 583–588, 2008). ARB enhanced natriuresis during the day, while BP was markedly lower during the night, resulting in the dipper pattern. In the present study, we examined whether the suppression of tubular sodium reabsorption, similar to the action of diuretics, was the mechanism by which ARB normalized the circadian BP rhythm. BP and glomerulotubular balance were compared in 41 patients with chronic kidney disease before and during ARB treatment with olmesartan once a day for 8 wk. ARB increased natriuresis (sodium excretion rate; UNaV) during the day (4.5 ± 2.2 to 5.5 ± 2.1 mmol/h, P = 0.002), while it had no effect during the night (4.3 ± 2.0 to 3.8 ± 1.6 mmol/h, P = 0.1). The night/day ratios of both BP and UNaV were decreased. The decrease in the night/day ratio of BP correlated with the increase in the daytime UNaV (r = 0.42, P = 0.006). Throughout the whole day, the glomerular filtration rate (P = 0.0006) and tubular sodium reabsorption (P = 0.0005) were both reduced significantly by ARB, although UNaV remained constant (107 ± 45 vs. 118 ± 36 mmol/day, P = 0.07). These findings indicate that the suppression of tubular sodium reabsorption, showing a resemblance to the action of diuretics, is the primary mechanism by which ARB can shift the circadian BP rhythm into a dipper pattern.

The circadian rhythm of BP exhibits a nondipper pattern in sodium-sensitive hypertension. Furthermore, we showed that sodium intake restriction (36) and diuretics (38) restored the circadian rhythm into a dipper pattern. In primary aldosteronism, both sodium intake restriction and adrenalectomy normalized the circadian BP rhythm from a nondipper to a dipper pattern (39). These findings consistently indicate the importance of the role of sodium retention in the genesis of the nondipper pattern of the circadian BP rhythm (18, 20). Recently, we found that an ANG II receptor blocker (ARB), olmesartan, also restored the circadian BP rhythm (12). ARB enhanced natriuresis during the day, while BP was markedly lowered during the night, resulting in the dipper pattern (12). However, in the previous study, there remained uncertainty regarding the contribution of the increase in natriuresis to the restoration of the nondipper BP rhythm. In the present study, we examined whether the suppression of tubular sodium reabsorption was the mechanism underlying the effect of ARB, similar to diuretics, to normalize the circadian BP rhythm.

MATERIALS AND METHODS

Patients. Forty-one patients with chronic kidney disease (CKD; 27 men and 14 women; aged 17–75 yr with a mean age of 44 ± 17 yr; body mass index: 23.2 ± 3.1 kg/m²; body weight: 62.7 ± 10.9 kg) were studied at the Nagoya City University Hospital. CKD was defined according to the Kidney Disease Outcomes Quality Initiative (K/DOQI) criteria (28). The subjects with stage 1 and 2 CKD were diagnosed as having CKD due to persistent albuminuria with a urinary albumin-creatinine ratio >300 mg/g, and/or glomerular hematuria. Patients with diabetic nephropathy or nephrotic syndrome were not included. Patients who were undergoing treatment with antihypertensive agents or diuretics were excluded. All participants were enrolled consecutively after obtaining informed consent between February 2009 and February 2010. Twenty-six subjects had glomerulonephritis, and 15 had nephrosclerosis. The study was approved by the ethics review committee of Nagoya City University Graduate School of Medical Sciences (no. 474) and was conducted in accordance with the Declaration of Helsinki, as published previously (10–12).

Study protocol. The subjects received nutritional instructions to eat a regular sodium diet containing <8 g/day of salt for at least 4 wk before enrollment and were asked to get up at 0600 and start bed rest at 2100. No additional medications or changes in the dosages of concomitant drugs were allowed throughout the study period. After the baseline examination, the participants received single daily doses of the ARB olmesartan in the morning. The dose of olmesartan was increased to achieve BP <130/80 mmHg or to reduce proteinuria.

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At the baseline and 8 wk after the treatment with ARB, 24-h BP monitoring and urinary sampling for both daytime (0600–2100) and nighttime (2100–0600) were repeated on the last day of a 7-day hospitalization period, during which diets including 7 g/day of salt were served, to compare the circadian rhythms of BP and natriuresis (sodium excretion rate; UNaV). BP was monitored noninvasively every 30 min with a validated automatic device (model ES-H531, Terumo, Tokyo, Japan). The BP values were not considered valid for analysis if data were missing for 2 h continuously, or if the patients awoke during the night and had difficulty falling asleep again. Mean arterial pressure (MAP) was calculated as the diastolic BP plus one-third of the pulse BP. Daytime BP was calculated as the average of the 30 readings between 0600 and 2100, whereas nighttime BP was the average of the remaining 18 readings. A decline in MAP during the nighttime compared with the daytime mean values was defined as the nocturnal BP dip.

Day and night urine samples were combined to calculate 24-h creatinine clearance as a measure of the glomerular filtration rate (GFR). Blood samples were collected at 0600 to measure serum creatinine and sodium (SNa) concentrations before and during ARB treatment. Blood samples for the evaluation of plasma renin activity (PRA), plasma aldosterone concentration (PAC), and ANG II were centrifuged at 3,000 rpm for 10 min at 4°C, and the plasma samples were frozen immediately and stored at −35°C until assay. The plasma levels of PRA, PAC, and ANG II were then assayed by radioimmunoassay at an external analysis center for medical science (SRL, Hachioji, Japan). The amount of sodium filtered from the glomerulus and loaded to renal tubules was calculated as the product of SNa and GFR, while the amount of sodium reabsorbed by renal tubules (TNa) was calculated as the difference between the amounts of filtered sodium load and urinary sodium excretion.

Statistical analysis. The results are expressed as means ± SD. The significance of differences in parameters between baseline and ARB treatment was examined by Student’s t-test for paired samples. Correlations among variables were evaluated by the least-squares method. Relationships between the changes in variables were analyzed by linear regression through the origin. P values <0.05 were considered statistically significant.

RESULTS

Eight-week treatment with the ARB olmesartan (5–40 mg once a day) administered in the morning lowered the systolic and diastolic BP during both day and night (Table 1). The nocturnal BP dip was increased (4.9 ± 10 to 9.6 ± 6.2 mmHg).

Table 1. Renal function and blood pressure before and during ARB treatment

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>P Value</th>
<th>ARB</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNa, mg/dl</td>
<td>1.6 ± 2.1</td>
<td>0.3</td>
<td>1.7 ± 2.3</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>131 ± 17</td>
<td>&lt;0.0001</td>
<td>120 ± 18</td>
</tr>
<tr>
<td>Night</td>
<td>125 ± 22</td>
<td>&lt;0.0001</td>
<td>109 ± 22</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>80 ± 12</td>
<td>&lt;0.0001</td>
<td>75 ± 12</td>
</tr>
<tr>
<td>Night</td>
<td>76 ± 13</td>
<td>&lt;0.0001</td>
<td>66 ± 13</td>
</tr>
<tr>
<td>UNaV, mmol/h</td>
<td>4.5 ± 2.2</td>
<td>0.002</td>
<td>5.5 ± 2.1</td>
</tr>
<tr>
<td>Night</td>
<td>4.3 ± 2.0</td>
<td>0.1</td>
<td>3.8 ± 1.6</td>
</tr>
<tr>
<td>Night/day ratio</td>
<td>0.95 ± 0.10</td>
<td>0.0001</td>
<td>0.89 ± 0.07</td>
</tr>
<tr>
<td>BP</td>
<td>1.10 ± 0.60</td>
<td>0.0002</td>
<td>0.80 ± 0.44</td>
</tr>
</tbody>
</table>

Values are means ± SD (n = 41). ARB, angiotensin receptor blocker; SNa, serum creatinine concentration; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial blood pressure; UNaV, urinary sodium excretion rate.

The glomerulotubular balance of sodium before and during ARB treatment is summarized in Table 2. GFR (P = 0.0006) was increased during the day (4.5 ± 2.2 to 5.5 ± 2.1 mmol/h, P = 0.002) but remained unchanged during the night (4.3 ± 2.0 to 3.8 ± 1.6 mmol/h, P = 0.1). Consequently, the night/day ratios of both MAP and UNaV were decreased. The lowering of nighttime MAP (r = 0.37, P = 0.02) and the decrease in the night/day ratio of MAP (r = 0.42, P = 0.006) both correlated with the increase in daytime UNaV (Fig. 1). In addition, the decrease in the night/day ratio of MAP correlated directly with the baseline night/day ratios of MAP (r = 0.73, P < 0.0001), although it did not correlate with the decrease in nighttime UNaV (r = 0.19, P = 0.2). The increase in nocturnal BP dip also correlated positively with the increase in daytime UNaV (r = 0.37, P = 0.02), but not with the decrease in nighttime UNaV (r = 0.14, P = 0.4).

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Fig. 1. Relationships of the change in the daytime natriuresis with the changes in the nighttime mean arterial pressure (MAP) and its night/day ratio. Changes in daytime natriuresis (ΔDaytime UNaV, mmol/h) correlated inversely with the changes in both nighttime mean arterial pressure (ΔMAP, mmHg; top) and night/day ratio of MAP (ΔNight/day ratio of MAP; bottom).

P = 0.001). UNaV was increased during the day (4.5 ± 2.2 to 5.5 ± 2.1 mmol/h, P = 0.002) but remained unchanged during the night (4.3 ± 2.0 to 3.8 ± 1.6 mmol/h, P = 0.1). Consequently, the night/day ratios of both MAP and UNaV were decreased. The lowering of nighttime MAP (r = 0.37, P = 0.02) and the decrease in the night/day ratio of MAP (r = 0.42, P = 0.006) both correlated with the increase in daytime UNaV (Fig. 1). In addition, the decrease in the night/day ratio of MAP correlated directly with the baseline night/day ratios of MAP (r = 0.73, P < 0.0001), although it did not correlate with the decrease in nighttime UNaV (r = 0.19, P = 0.2). The increase in nocturnal BP dip also correlated positively with the increase in daytime UNaV (r = 0.37, P = 0.02), but not with the decrease in nighttime UNaV (r = 0.14, P = 0.4).

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and T\textsubscript{Na} (P = 0.0005) were both significantly reduced by ARB, although the 24-h U\textsubscript{Na}V remained constant (107 ± 45 vs. 118 ± 36 mmol/day, P = 0.07), indicating that a steady-state sodium balance had been achieved. Olmesartan increased PRA (1.3 ± 0.8 to 8.1 ± 10.4 ng·ml\textsuperscript{-1}·h\textsuperscript{-1}, P < 0.0001), decreased PAC (98 ± 67 to 80 ± 58 pg/dl, P = 0.04), and increased ANG II (10 ± 5 to 22 ± 20 pg/ml, P < 0.0001). The increase in PRA (r = 0.27, P = 0.09), decrease in PAC (r = 0.07, P = 0.7), and increase in ANG II (r = 0.15, P = 0.3) did not correlate with the increase in daytime U\textsubscript{Na}V.

**DISCUSSION**

The present study demonstrated that an ARB, olmesartan, restored and shifted the circadian BP rhythm from a non-dipper to a dipper pattern, consistent with the findings of our previous study (12). However, in the previous study, there remained two potential explanations for the shift in the circadian BP rhythm. First, ARB suppressed tubular sodium reabsorption, similar to diuretics, which have been clearly demonstrated to restore the rhythm. Second, ARB might primarily lower nighttime BP, resulting in reduced GFR and natriuresis during the night. It is possible that the resultant sodium retention during the night caused natriuresis during the day. In any case, natriuresis can be enhanced during the day by ARB, and in fact the increase in U\textsubscript{Na}V during the day correlated significantly with the decrease in the night/day ratio of the MAP. However, in the previous study, it remained difficult to understand how sodium balance could be maintained at a lower BP, despite the reduced GFR. If GFR is primarily reduced functionally, sodium balance becomes positive as long as tubular sodium reabsorption remains constant, resulting in elevation of the BP. Therefore, BP and GFR must return to their original levels in the steady state. On the other hand, if tubular sodium reabsorption is primarily suppressed by ARB, sodium balance becomes negative as long as GFR remains normal, resulting in lowering of the BP and a reduction of the GFR in the steady state (1, 9, 34). Therefore, in the present study, we further investigated theglomerulotubular balance of sodium. Our data regarding the steady state of sodium balance shown in Table 2 are consistent with the first possible explanation. From the above discussion, we believe that ARB normalizes the circadian BP rhythm by suppressing tubular sodium reabsorption.

Similar sequences of changes in sodium balance have been reported in animal experiments. Chronic blockade of ANG II formation resulted in enhanced natriuresis and lowering of the BP and GFR during sodium deprivation (15). Furthermore, ANG II receptor AT\textsubscript{1} knockout mice also exhibited enhanced natriuresis along with decreased BP (30). These findings from animal experiments strongly suggest that ARB primarily suppresses tubular sodium reabsorption and that the resulting volume depletion may be one of the important mechanisms for lowering of BP. Since ANG II stimulates tubular sodium reabsorption at various segments from the proximal to distal tubules, ARB are well known to suppress tubular sodium reabsorption in vitro (5). However, the precise mechanisms as to how ARB causes natriuresis in vivo remain unknown (5).

It is well accepted that inhibitors of the renin-angiotensin system (RAS), including ARB, lower the glomerular capillary pressure and GFR (2, 40), resulting in renal protection (3, 25, 26, 31). Reduction in glomerular capillary pressure by RAS inhibitors is often explained mostly by the predominant dilatation of efferent arterioles located after the glomerulus, and the inhibitors of RAS are considered as afterload reduction therapy (7), while restriction of protein intake is considered as preload reduction therapy, because it constricts the preglomerular afferent arterioles located before the glomerulus (7). However, as discussed above, if the GFR is primarily reduced, sodium balance becomes positive, resulting in restoration of BP, glomerular capillary pressure, and GFR to their original levels. Therefore, it seems impossible to maintain these parameters at the lower levels in the steady state. Instead, we believe that suppression of renal tubular reabsorption of sodium may be the primary mechanism for RAS inhibitors to lower them.

It is also well known that inhibitors of RAS enhance BP sodium sensitivity (6, 14, 23), which is mostly determined by the glomerulotubular balance of sodium (21). In fact, the increased tubular reabsorption of sodium by primary aldosterone-remotes enhances sodium sensitivity (24), while the decreased tubular reabsorption by diuretics suppresses sodium sensitivity (1, 34). The opposite effect of RAS inhibitors on sodium sensitivity compared with that of diuretics often causes us to neglect the tubular effect of RAS inhibitors. However, the sodium sensitivity of BP is also determined by the intactness of feedback control of the RAS (14). If feedback control is disrupted, by ANG II infusion or RAS inhibitors, sodium sensitivity is enhanced (6, 14). Thus RAS inhibitors enhance sodium sensitivity, independent of the effect on tubular sodium reabsorption. It has been established that RAS inhibitors suppress the tubular reabsorption of sodium in various segments of the nephron (5).

Polónia et al. (32) reported that treatment with the ARB irbesartan once in the morning restored the non-dipper pattern of circadian BP rhythm to a dipper pattern by an 18/10-mmHg reduction in nighttime BP. Although they failed to show causality in this relationship, they believed that the restoration of circadian BP rhythm was due to the reduction in vascular resistance, which might be caused by the increase in potassium balance and suppression of the renin-angiotensin-aldosterone system, rather than an increase in natriuresis. However, in their study, GFR was reduced by ARB, as observed in our study, and 24-h U\textsubscript{Na}V remained unchanged. These findings could not be explained by primary reductions in vascular resistance and GFR, as discussed above. We believe their data were consistent with primary inhibition of tubular sodium reabsorption.

Impaired renal sodium excretion capacity causes sodium retention, leading to pressure overload on the glomerular hydrostatic pressure, as well as the systemic circulation. Indeed, we (27) and others (13, 17, 29, 35) have reported significant relationships between the sodium-sensitive type of hypertension or nondipper circadian BP rhythm and renal dysfunction, as well as cardiovascular events. The MAPEC study (33) showed that the decrease in the prevalence of a nondipper pattern was accompanied by a reduction in cardiovascular morbidity and mortality. Based on these findings, we speculate that sodium retention is the key to connect CKD and cardiovascular events, and ARB has the potential to sever these connections.

In conclusion, RAS inhibitors, including ARBs, appear to suppress tubular sodium reabsorption. This may be the primary mechanism responsible for shifting the circadian BP rhythm from a non-dipper to a dipper pattern. Although it is not easy to
elucidate their diuretic effects in clinical practice, this is the first study to demonstrate findings on the glomerulotubular balance of sodium that are consistent with the findings shown in animal experiments. To determine the characteristic effect of olmesartan, further evaluation, replacing olmesartan with other ARBs and measuring plasma ANG 1–7 levels, are necessary. As mentioned above, ARBs can inhibit sodium reabsorption, which is inappropriately stimulated by ANG II via the ANG II type 1 receptor, in animal models. However, further studies are required to clarify under what pathophysiological conditions ARBs can exert an action resembling that of diuretics in a clinical scene.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

REFERENCES


