The Role of Renal Natriuretic Depressor Systems on Hypertensive Mechanisms in Reduced Renal Mass Hypertensive Rats

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The pathophysiological role of renal natriuretic depressor systems and endogenous digitalis like factor (EDLF) on blood pressure (BP) elevation was studied in reduced renal mass rats (RRM) with saline loading for a model of volume dependent hypertension. Fifty-four male Sprague-Dawley rats were operated on to remove varying proportions of their kidney mass (5/6 RRM, n = 13; 4/6 RRM, n = 16; 3/6 RRM, n = 12) or sham operated (control, n = 13). They were given 1% saline to drink for 4 weeks. BP was elevated significantly at the 1st week in 5/6 RRM and continued to increase until the 4th week, but this was not seen in the other 3 groups. Urine volume (UV) and urinary sodium excretion (UNaV) increased after saline loading in all groups. Urinary kallikrein excretion was significantly lower in order of the 5/6, 4/6 and 3/6 RRM at the basal state and after saline loading. A significant negative correlation was observed between urinary kallikrein and BP. Urinary PGE2 was increased in each RRM in order of the 5/6, 4/6 and 3/6 RRM groups. A significant positive correlation was observed between urinary PGE2 and BP, UV or UNaV. The basal urinary DA excretion was significantly lower in 3 RRMs than in the control. After saline drinking, urinary DA increased in 3 RRMs, while differences disappeared in the control and RRMs. Urinary EDLF increased immediately after the initiation of saline loading in all groups, except the control group, and returned to the basal level 2 weeks later in 3/6 and 4/6 RRM. Only in 5/6 RRM, the urinary EDLF remained higher than the basal level. A significant positive correlation was found between urinary EDLF and BP or UNaV. From these observations, it was suggested that 1) in 5/6 RRM, EDLF has an important role in the pathogenesis of hypertension, 2) suppressed renal kallikrein-kinin system may have something to do with the BP elevation, and 3) renal PGE2 and DA systems may act to compensate for sodium retention and BP elevation. (Hypertens Res 1995; 18 Suppl. I: S53-S57)

Key Words: hypertension, reduced renal mass rat, dopamine, kallikrein, prostaglandin E2, endogenous digitalis like substance

The etiology of human essential hypertension has defied precise understanding despite a large number of attempts at clarification. We have performed a series of experiments to investigate disturbances in sodium handling in essential hypertension, especially in low renin essential hypertension (1). Recently, we reported that decreases of urinary excretion of dopamine, kallikrein and prostaglandin (PG) E2, and augmented urine volume, excretions of sodium, kallikrein and PGE2, and fractional sodium excretion occurred in response to infused dopamine in essential hypertensives. These changes particularly stood out in the low renin group (1-3). Moreover, the suppression of the renal dopaminergic system was confirmed at the prehypertensive stage of essential hypertension (4). These studies suggest some kind of suppression of the renal natriuretic depressor systems composed of dopamine, kallikrein-kinin and PGE2 systems. This might be related to the disturbance of renal water-sodium handling in essential hypertension, especially in low renin essential hypertension.

It has been widely discussed whether chronic plasma volume expansion causes blood pressure elevation by increasing an unknown natriuretic hormone involved in the regulation of renal sodium excretion (5). Plasma extracts of volume-expanded subjects inhibit microsomal Na-K ATPase, and therefore, this natriuretic hormone has been called a endogenous digitalis-like factor (EDLF)(6). There is no doubt that EDLF is observed in human plasma (7, 8), and that plasma EDLF is elevated in patients with essential hypertension (9). From these findings, the possibility exists that a genetic disturbance of renal sodium handling may induce volume expansion, and this expanded plasma volume stimulates EDLF excretion, which results in natriuresis and an increase of peripheral vascular resistance (10, 11).

It is generally accepted that 5/6 RRM with high...
salt intake shows hypertension through volume expansion (12, 13). In the present study, RRM were employed as a sodium retention animal model, and the pathophysiological roles of renal natriuretic depressor systems and EDLF were investigated.

Materials and Methods

Fifty-four male Sprague-Dawley rats weighing 130 -150 g were divided into the following 4 groups. One third upper pole (4/6 RRM, n =16) or upper and lower poles (5/6 RRM, n =13) of the left kidney were resected. One week after the operation, the right kidney was removed in both groups. One week after a sham operation, the right kidney was resected (3/6 RRM, n=12) or a second sham operation was repeated in control rats (control n 13). Operations were performed under ether anesthesia. After the second operation, rats were housed in metabolic cages and fed regular rat chow throughout the experiments. All rats were kept under constant temperature (20°C) with lights on and off every 12 h. All rats were given tap water to drink for 1 week as a control interval before the experimental period. In the experimental period, all rats were given 1 % saline as drinking fluid until the end of the experiment. Urine was collected every 24 h for 2 days at the end of the control period, and at the end of the 1st, 2nd, 3rd and 4th weeks after starting 1% saline ingestion. Blood was taken from the abdominal aorta under ether anesthesia at the end of the experiment.

Urine volume and urinary sodium excretion remarkably increased during the first week after 1 % saline drinking in all groups, except for urine volume in the control, which had a slight increase (Table 1). In 3/6 and 4/6 RRM, both urine volume and urinary sodium excretion decreased after the 2nd week, while on the other hand, in 5/6 RRM, urine volume and urinary sodium excretion continued to increase until the 3rd week. Urine volume and urinary sodium excretion were higher in the order of 5/6, 4/6, 3/6 RRM and control throughout the experiment (Table 1). Only in 5/6 RRM, systolic blood pressure increased significantly at the 1st week after 1% saline drinking, and it continued to increase throughout the 4 weeks, but there was no significant change in systolic blood pressure in the other 3 groups (Table 2).

Results

Urine volume and urinary sodium excretion remarkably increased during the first week after 1 % saline drinking in all groups, except for urine volume in the control, which had a slight increase (Table 1). In 3/6 and 4/6 RRM, both urine volume and urinary sodium excretion decreased after the 2nd week, while on the other hand, in 5/6 RRM, urine volume and urinary sodium excretion continued to increase until the 3rd week. Urine volume and urinary sodium excretion were higher in the order of 5/6, 4/6, 3/6 RRM and control throughout the experiment (Table 1). Only in 5/6 RRM, systolic blood pressure increased significantly at the 1st week after 1% saline drinking, and it continued to increase throughout the 4 weeks, but there was no significant change in systolic blood pressure in the other 3 groups (Table 2).

Urine kallikrein excretion was significantly lower in every RRM group than in control at the basal state, in order of the 5/6, 4/6, 3/6 RRM and control throughout the experiment (Table 1). Only in 5/6 RRM, systolic blood pressure increased significantly at the 1st week after 1% saline drinking, and it continued to increase throughout the 4 weeks, but there was no significant change in systolic blood pressure in the other 3 groups (Table 2).
on urinary kallikrein excretion and urine volume or urinary sodium excretion.

On the other hand, urinary excretion of PGE2 was high in each group at the basal state (Fig. 2). After 1% saline administration, urinary PGE2 increased in all groups. The increments were largest in the 5/6, then in the 4/6, the 3/6 and control, in decreasing order (Fig. 2). Significant positive correlations were observed between urinary PGE2 and systolic blood pressure ($r = 0.482$, $p < 0.01$), and between urinary PGE2 and urine volume ($r = 0.783$, $p < 0.01$) or urinary sodium excretion ($r = 0.728$, $p < 0.01$) in all groups at control period and during saline loading.

Urinary dopamine excretion was significantly lower in the 3/6, 4/6 or 5/6 RRM than in the control at the basal state before saline loading (Fig. 3). One week after 1% saline loading, urinary excretion of dopamine increased somewhat in the 3/6 and 4/6 RRM groups, while it fell in the control, cancelling the significant difference between those two. The increases were never significant and fell to near the basal levels in the 3rd and 4th weeks. In the 5/6 RRM, urinary dopamine excretion was significantly increased at 1 and 2 weeks after saline loading. As a result, there were no differences in urinary dopamine excretion between 5/6 RRM and control after saline administration (Fig. 3).

Urinary EDLF was slightly, but significantly higher in 5/6 and 4/6 RRM at the end of the control period, during which all rats were given tap water to drink (Fig. 4). After 1% saline administration, urinary EDLF increased significantly in the 3/6, 4/6 and 5/6 RRM, but not in the control group. However by the 2nd week, urinary EDLF had returned to the basal level in 3/6 and 4/6 RRM (Fig. 4). In 5/6 RRM urinary EDLF remained higher than the basal and the control group levels throughout the experiment. No change was found in the control group (Fig. 4). There was a quite significant positive correlation between urinary EDLF and systolic blood pressure ($r = 0.343$, $p < 0.01$) and between urinary EDLF and urinary sodium excretion ($r = 0.744$, $p < 0.01$) in all groups at control period and during saline loading.

Table 2. Changes of Systolic Blood Pressure (SBP) in the Control Group and Each Reduced Renal Mass Rats (RRM) Group

<table>
<thead>
<tr>
<th>Group</th>
<th>Week</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tbody>
<tr>
<td>Control</td>
<td>0</td>
<td>136±3</td>
<td>141±2</td>
<td>138±2</td>
<td>140±2</td>
<td>138±3</td>
</tr>
<tr>
<td>3/6 RRM</td>
<td>1</td>
<td>136±2</td>
<td>140±2</td>
<td>140±2</td>
<td>144±3</td>
<td>155±2</td>
</tr>
<tr>
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<td>2</td>
<td>136±3</td>
<td>136±3</td>
<td>143±3</td>
<td>151±3</td>
<td>148±3</td>
</tr>
<tr>
<td>5/6 RRM</td>
<td>3</td>
<td>135±3</td>
<td>157±3*#</td>
<td>171±7**#</td>
<td>187±10**#</td>
<td>186±8**#</td>
</tr>
</tbody>
</table>

* $p<0.05$ vs. before,  ** $p<0.05$ vs. control.

Fig. 1. The changes in urinary kallikrein excretion (KAL) in the control, 3/6 RRM, 4/6 RRM and 5/6 RRM. RRM; reduced renal mass rats.

Fig. 2. The changes in urinary prostaglandin E2 excretion (PGE2) in the control, 3/6 RRM, 4/6 RRM and 5/6 RRM. RRM; reduced renal mass rats.

Fig. 3. The changes in urinary dopamine excretion in the control, 3/6 RRM, 4/6 RRM and 5/6 RRM. RRM; reduced renal mass rats.

Fig. 4. The changes in urinary endothelin peptide (EDLF) excretion in the control, 3/6 RRM, 4/6 RRM and 5/6 RRM. RRM; reduced renal mass rats.
during saline loading.

At the end of the experiment, the serum creatinine observed between urinary PGE$_2$ and blood pres-
rats than in control rats. The authors previously reported that a transient increase of EDLF in 4/6 and 3/6 RRM rats failed to elevate the blood pressure. In this study, increased EDLF was found in established 5/6 RRM hypertensive rats. Although urinary EDLF excretion increased significantly in 3/6 and 4/6 RRM rats during the first week, they did not show hypertension. On the other hand, in 5/6 RRM rats urinary EDLF continued to increase during the 1% saline drinking. Furthermore, in 5/6 RRM rats, systolic blood pressure was raised significantly at the first week and continued to be elevated throughout the experiment. This observation suggests that high EDLF levels might maintain high blood pressure in 5/6 RRM hypertensive rats. The significant positive correlation between EDLF and systolic blood pressure seems to support this conclusion as well. Consequently, there was a significant positive correlation between EDLF and systolic blood pressure or UNaV. These results indicate that urinary EDLF seems to be related to both the elevation of blood pressure and the augmentation of sodium excretion in 5/6 RRM rats.

From these data, it was concluded that in RRM hypertensive rats, the renal dopaminergic system may compensate for the blood pressure increase and sodium retention, and that EDLF may be necessary to induce blood pressure elevation in 5/6 RRM hypertensive rats.

References

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