Inhibitory effect of potassium on blood pressure in DOCA salt hypertension in rats

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Abstract. The present study was performed to assess the influence of potassium on blood pressure in deoxycorticosterone (DOCA) salt hypertensive rats. The effects of potassium administration on the systolic blood pressure, fluid intake, urine volume, excretion of sodium and potassium, serum sodium and potassium, plasma renin activity (PRA) and plasma aldosterone concentration (PAC) were investigated both during the first 2 weeks of development of DOCA salt hypertension and during the next 2 weeks of established DOCA salt hypertension. Potassium administration prevented the development of DOCA salt hypertension and reduced the blood pressure in established DOCA salt hypertension. Fluid intake, urine volume, and excretion of sodium and potassium appeared to be markedly increased in rats treated with potassium. The levels of serum sodium and potassium were unchanged by potassium loading. Both the PRA and PAC which were suppressed in DOCA salt hypertensive rats, were reversed in rats treated by potassium loading. It is suggested that the elevation of blood pressure may be prevented and the increased blood pressure reduced mainly by the diuresis and natriuresis caused by potassium loading.

In contrast to sodium, potassium is thought to exert a preventive action on the development of hypertension (Meneely & Battarbee 1976; Nutrition Review 1962). Although the precise mechanism of this antihypertensive action of potassium remains controversial, the natriuretic properties of potassium or the direct action of potassium on the vascular wall are thought to play an important role

(Young et al. 1976; Chen et al. 1972). In fact, Dahl et al. (1972) have reported that the dietary Na/K molar ratio is an important determinant of the severity or extent of development of salt induced hypertension.

In the present study, the depressor effect of potassium in established DOCA salt hypertension and the preventive effects of potassium on the development of DOCA salt hypertension, were studied in rats.

Materials and Methods

Two series of experiments were performed with 72 rats.

Experiment 1

Forty-eight male Wistar rats, weighing 130–140 g, were used. After right nephrectomy under ether anaesthesia, the rats were divided into four groups, each consisting of 12 rats, and the following procedures were carried out.

Rats of group 1 formed the control. All the rats in this group were given tap water to drink ad libitum, and were injected im with 0.5 ml of sesame oil daily for 14 days. Rats in group 2 were injected with 1 mg of DOCA daily for 14 days and given 1% NaCl to drink. Rats in group 3 were also injected with 1 mg of DOCA daily for 14 days but were given a mixed solution of 1% NaCl and 0.5% KCl to drink.

All rats were fed on a normal diet containing Na 0.28 g/100 ml and K 0.77 g/100 ml. Each rat was individually caged in temperature- and humidity-controlled quarters. The daily fluid intake and urine volume were measured in all rats during the study. The body weight was recorded once a week. The systolic blood pressure was measured twice a week by a tail-cuff plethysmographic
method. On the 7th experimental day, half of the rats were sacrificed by decapitation, and on the 14th experimental day, the remaining rats were sacrificed by decapitation. The blood was collected into chilled test tubes.

Experiment II

Twenty-four male Wistar rats, weighing 130–140 g, were used. After right nephrectomy under ether anesthesia, the rats were divided into two groups. The rats in both groups were injected im with 1 mg of DOCA daily for 4 weeks. Rats of group 1 were given 1% NaCl to drink ad libitum during the study, while rats of group 2 were given 1% NaCl to drink for the first 2 weeks and were then switched to a mixed solution of 1% NaCl and 0.5% KCl.

All rats were fed on a normal diet containing Na 0.28 g/100 ml and K 0.77 g/100 ml. Each rat was individually caged under the same conditions as in Experiment I. The daily fluid intake and urine volume were measured in all rats during the study. The body weight was checked once a week. The systolic blood pressure was measured twice a week by the same method as in Experiment I. Half of the rats in both groups were decapitated on the 14th experimental day, and the others were sacrificed by decapitation on the 28th experimental day. PRA was determined by the method of Skinner (1967) and PAC was measured by radioimmunoassay. Urinary and serum electrolytes were measured with a flame photometer.

Error limits were expressed as ± SD, and Student's t-test was employed to determine the statistical significance.

Results

Experiment I

Changes in blood pressure. The blood pressure increased from 105 ± 3 to 150 ± 10 mmHg in rats of group 2 (DOCA plus 1% NaCl). However, in rats of group 3 (DOCA plus 1% NaCl and 0.5% KCl), the elevation of blood pressure was significantly less than that in the rats of group 2 on both the 7th day (P < 0.05) and 14th day (P < 0.001) (Fig. 1). In rats of group 4 (1% NaCl and 0.5% KCl), the changes in blood pressure were not significant, being just as in rats of group 1 (control).

Changes in body weight. Although there was no difference in body weight among the groups at the beginning of the experiment, the growth of rats in

Effect of potassium loading on the systolic blood pressure in rats. In rats given DOCA plus NaCl, the blood pressure increased progressively. In rats given DOCA plus NaCl and KCl, there was only a slight increase in blood pressure. In rats given NaCl and KCl, and in control rats, no increment of blood pressure was observed. There were significant differences in the blood pressure between two groups, in rats, given DOCA plus NaCl with or without KCl, on the 7th day (P < 0.05) and on the 14th day (P < 0.001), respectively. Values are means and bars indicate SD.
Effects of potassium administration on body weight, serum electrolytes, PRA and PAC during the development of DOCA salt hypertension in rats.

<table>
<thead>
<tr>
<th>Groups</th>
<th>7th day, serum electrolytes</th>
<th>14th day, serum electrolytes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ABW (g)</td>
<td>Na (mEq/l)</td>
</tr>
<tr>
<td>Control (n = 6)</td>
<td>+36.6</td>
<td>140.0</td>
</tr>
<tr>
<td>DOCA plus NaCl (n = 6)</td>
<td>+43.3</td>
<td>142.8</td>
</tr>
<tr>
<td>DOCA plus NaCl and KCl (n = 6)</td>
<td>-18.6</td>
<td>146.3</td>
</tr>
</tbody>
</table>

ΔBW: increase or decrease of body weight. Values are means ± SD. N = number of animals.
* Significantly different from control P < 0.01.

Group 3 (DOCA plus NaCl and KCl) and group 4 (NaCl and KCl) was significantly smaller than that in rats of group 1 (control) and group 2 (DOCA plus NaCl) (P < 0.01) (Table 1).

Changes in fluid intake, urine volume and electrolytes. In rats of group 2 (DOCA plus NaCl), both the fluid intake and urine volume gradually increased during the first week and then reached a plateau in the next week. In rats of group 3 (DOCA plus NaCl and KCl), both the fluid intake and urine volume were initially less than those in group 2, but gradually increased and finally exceeded those in the DOCA salt hypertensive rats (Fig. 2: upper panel). Although the urinary excretion of sodium and potassium in rats of group 2 (DOCA plus NaCl) increased gradually during the study, the urinary excretion of these ions were greater in group 3 (DOCA plus NaCl and KCl) and group 4 (NaCl and KCl) (Fig. 2: lower panel). There was no marked differences in serum sodium and potassium among the groups (Table 1).

PRA and PAC. The PRA was significantly reduced in group 2 (DOCA plus NaCl), but was significantly increased in group 3 (DOCA plus NaCl and KCl) and group 4 (NaCl and KCl) on both the 7th day (P < 0.01) and 14th day (P < 0.01). However, after the 14th day, the PRA in group 3 returned to the levels observed in group 2. The PRA in group 4 still remained at high levels. The results for PAC were almost similar to those for PRA in all the groups (Table 1).

Experiment II

Changes in blood pressure. In this experiment, 0.5% KCl was given to one group of rats (group 2) after hypertension had developed following the administration of DOCA and NaCl. Such potassium loading reduced the elevated blood pressure and prevented any further elevation of blood pressure, as shown in Fig. 3.

Changes in body weight. The administration of potassium resulted in a significant reduction of body weight (P < 0.01) (Table 2).

Changes in fluid intake, urine volume and electrolytes. With the initiation of potassium loading, the fluid intake and urine volume decreased transiently, but 2 days later they began to increase again (Fig. 4: upper panel). When the potassium loading was started, the urinary excretion of sodium decreased...
Upper panel: Changes in fluid intake and urine volume. In rats treated with DOCA plus NaCl, both fluid intake and urine volume have gradually increased during the first week and then reached a plateau in the next week. In both rats treated with DOCA plus NaCl and KCl and with NaCl and KCl, both fluid intake and urine volume have progressively increased during the experiment. Values are means and bars indicate SD.

Lower panel: Daily urinary excretion of sodium and potassium. In rats treated with DOCA plus NaCl, urinary excretion of sodium and potassium increased gradually during the study. In both rats treated with DOCA plus NaCl and KCl and with NaCl and KCl urinary excretion of sodium and potassium was massive above the rats treated with DOCA plus NaCl. Values are means and bars indicate SD.
Effect of potassium loading on the systolic blood pressure in rats. All rats were treated with DOCA plus NaCl during the first 2 weeks. In rats given DOCA plus NaCl, the blood pressure increased progressively. On the other hand, the administration of potassium markedly prevented the elevation of the blood pressure in DOCA salt hypertension. There were significant differences in the blood pressure between two groups — rats given DOCA plus NaCl with or without KCl — on the 21st day ($P < 0.01$) and on the 28th day ($P < 0.001$). Values are means and bars indicate SD.

Transiently in accordance with the reduction in fluid intake, but after that the urinary excretion of sodium began to increase with the subsequent increase in urinary excretion of potassium. Thus, on the 28th experimental day, the urinary excretion of sodium in group 2 (DOCA plus NaCl and KCl) was far greater than that in group 1 (DOCA plus NaCl) (Fig. 4: lower panel). There were no significant differences in serum electrolytes between the two groups (Table 2).

### Table 2.

Effects of potassium administration on body weight, serum electrolytes, PRA and PAC during the established DOCA salt hypertension in rats.

<table>
<thead>
<tr>
<th>Groups</th>
<th>14th day, serum electrolytes</th>
<th>28th day, serum electrolytes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BW (g)</td>
<td>Na (mEq/l)</td>
</tr>
<tr>
<td>DOCA plus NaCl</td>
<td>172.3 ± 3.2</td>
<td>142.3 ± 3.4</td>
</tr>
<tr>
<td>(n = 6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOCA plus NaCl and KCl</td>
<td>176.5 ± 3.9</td>
<td>144.6 ± 4.6</td>
</tr>
<tr>
<td>(n = 6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD. n = Number of animals.

* Significantly different between rats treated without KCl and those with KCl, $P < 0.01$. 

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**Fig. 3.**

Effect of potassium loading on the systolic blood pressure in rats. All rats were treated with DOCA plus NaCl during the first 2 weeks. In rats given DOCA plus NaCl, the blood pressure increased progressively. On the other hand, the administration of potassium markedly prevented the elevation of the blood pressure in DOCA salt hypertension. There were significant differences in the blood pressure between two groups — rats given DOCA plus NaCl with or without KCl — on the 21st day ($P < 0.01$) and on the 28th day ($P < 0.001$). Values are means and bars indicate SD.
Upper panel. Changes in fluid intake and urine volume. All rats were treated DOCA plus NaCl during the first 2 weeks. After the initiation of the administration of potassium, there was a transient decrease of fluid intake and urine volume. However, urine volume in the rats given KCl has gradually increased over that in the DOCA salt hypertensive rats. Values are means and bars indicate SD.

Lower panel. Daily urinary excretion of sodium and potassium. All rats were treated with DOCA plus NaCl during the first 2 weeks. Administration of potassium resulted in transiently decreased urinary excretion of sodium and potassium and then it induced marked increment of urinary excretion of potassium. Urinary excretion of sodium was slightly different between the rats treated with or without KCl. Values are means and bars indicate SD.
**PRA and PAC.** Although PRA and PAC were slightly suppressed by the administration of DOCA plus NaCl, the values became markedly increased by the end of the 2nd week of continued KCl administration in addition to DOCA plus NaCl (Table 2).

**Discussion**

The findings of this study indicate that potassium loading can reduce blood pressure in established DOCA salt hypertension and can prevent the development of DOCA salt hypertension in rats. These findings are, however, in contrast to a previous study (Rosenman et al. 1951), in which potassium loading accentuated the pressor effect of DOCA and there was no significant difference in the elevated blood pressure between the administration of DOCA with 1% NaCl and that with 0.5% KCl, at least in the first 4 weeks of the experiment. Although it is difficult to explain the discrepancy between their results and ours, the difference in the experimental procedures is probably related to that they used un nephrectomized rats and gave 0.5% KCl solution alone.

Several hypotheses have been proposed concerning the mechanism by which blood pressure is reduced by potassium loading (Young et al. 1976; Chen et al. 1972). One possibility is a direct action by potassium ion on the vascular bed. Many studies have suggested that infusion of potassium ion decreased the vascular tone in vivo (Murray & Sparks 1978; Frolich et al. 1962), and K-free solution produced a sustained contraction in the isolated guinea pig (Brünger et al. 1976) and rat mesenteric arteries (Karaki & Ura kawa 1979). Potassium ion also inhibited the vascular contraction induced by norepinephrine in a dose-dependent manner (Kondo et al. 1979). Therefore, when a large dose of potassium is administered, these direct effects of potassium ion on the vascular bed should be considered even in the in vivo state.

Another mechanism by which potassium loading may reduce blood pressure is increased natriuresis. It is reported that potassium salts were first used as diuretics in clinical medicine in 1679 (Willis 1679). Also Addison (1928) reported that potassium administration could reduce elevated blood pressure in man, while Keith & Binger (1935) reported that potassium salts can be used under various conditions as diuretics without toxicity. Recently, Dahl et al. (1972) found that potassium loading can prevent the development of salt hypertension, and Young et al. (1976) found that chronic administration of potassium salts induced a negative sodium balance in dogs and reduced the blood pressure in chronically adrenalectomized dogs maintained on fixed levels of aldosterone.

In the present DOCA salt hypertension, potassium loading also increased natriuresis, both when it was given simultaneously with DOCA plus NaCl from the beginning of the experiment, and when it was given after DOCA salt hypertension had been established. The findings that the reduction in blood pressure by potassium loading was slight in rats with established DOCA salt hypertension indicated that the antihypertensive effects of potassium loading are not so strong or that the hypotensive effects tend to be limited to certain types of hypertension. It may also be suggested that a mechanism other than salt retention is operating in established DOCA salt hypertension, since remarkable natriuresis was observed on potassium loading.

Increase in body weight was not observed in the rats treated with potassium loading. One of the possible causes of this phenomenon is probably due to massive diuresis and slight reduction in food intake.

The mechanisms governing the natriuresis induced by potassium loading also remain controversial. Young et al. (1976) demonstrated that natriuresis by potassium loading is observed with an increase in the plasma potassium concentration, but in the present experiment there was no significant increase in serum potassium. Since it is known that the potassium concentration in the tubular fluid increases markedly with potassium loading, it is presumed that sodium re-absorption in the tubules is inhibited by the increased amounts of potassium (Kahn & Bohrer 1967; Wright et al. 1971).

In addition to the natriuresis induced by potassium loading and the possible direct action of potassium ion on the vascular bed, effects of potassium loading on the renin-angiotensin-aldosterone system are also thought to be related to the control of blood pressure (Brunner et al. 1970; Boyd et al. 1971; Dluhy et al. 1974). However, the findings that the suppression of PRA and PAC by DOCA and salt was reversed, and that elevated blood pressure was alleviated by potassium loading may suggest that changes in the renin-angiotensin-aldosterone system are secondary to natriuresis.
In conclusion, therefore, it is thought on the basis of our study that the elevation of blood pressure in DOCA salt hypertension may be prevented and the increased blood pressure reduced mainly by the diuresis and natriuresis caused by potassium loading.

References


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