Altered Secretion of Corticosteroids and Prolactin in Adrenal Regeneration Hypertensive Rats

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Abstract. To assess the possible role of mineralocorticoids in the onset and maintenance of hypertension in adrenal regeneration hypertensive (ARH) rats, the change in plasma mineralocorticoids, with adrenal regeneration after enucleation in ARH rats was investigated and compared with those in unilaterally nephroadrenalectomized, 1% saline-fed (UNA) rats, sham-operated, 1% saline-fed (1% NaCl) rats and water-fed (water) rats. Plasma aldosterone was determined by RIA and the other mineralocorticoids were measured by HPLC. How plasma PRL, a marker of central dopaminergic activity, affected aldosterone secretion was determined by RIA. In ARH, plasma corticosterone (B), 18-OH-DOC and aldosterone levels 2 weeks after operation were as low as 20-30% of corresponding values, but the plasma DOC level was almost 100% of the corresponding value in the other groups. Four weeks after operation plasma B increased to a level comparable with that in the other groups and the plasma aldosterone level remained low. However, plasma DOC and 18-OH-DOC levels 4 weeks after operation were as high as 120-200% of corresponding values in the other groups. Six weeks after operation, the plasma aldosterone level returned to a value comparable with that in UNA and 1% NaCl and plasma DOC and 18-OH-DOC levels returned to corresponding values in the other groups. The plasma PRL level 4 weeks after operation was significantly lower in ARH than in the other groups. These results suggest that transient DOC and 18-OH-DOC increases observed in ARH may be important in the onset of hypertension, while other factors may be involved in its maintenance and that the transient central dopaminergic hyperactivity observed in ARH may be responsible for a delayed return from aldosterone deficiency.

Key words: Adrenal regeneration hypertension, Mineralocorticoids, Prolactin, Central dopaminergic activity.

SKELTON [1] induced hypertension in rats by feeding them with 1% saline following heminephroadrenalectomy coupled with contralateral adrenal enucleation. This hypertension, called adrenal regeneration hypertension (ARH), develops in 3 or 4 weeks postoperatively as adrenal regeneration progresses. The pathogenesis and pathophysiology of ARH has been linked to the presence of excessive secretion, from the regenerated adrenal, of corticosteroids (CSs) [2-5], which are responsible for sodium retention or changes in the steroid spectrum [6], but the complete mechanism remains to be clarified. In the present study, we monitored the plasma concentrations of various CSs, particularly mineralocorticoids (MCs), in rats receiving operation to induce ARH, and then the results were compared with those obtained in control rats.

Secretion of aldosterone has been reported to decrease in ARH rats [2, 7]. To determine whether the central dopaminergic (DA) activity, a factor which regulates aldosterone secretion [8, 9], is involved in this decrease, the plasma prolactin (PRL) concentration was monitored as an index of central DA in this study.
Materials and Methods

Animals and treatment

Young male Wistar rats, weighing between 80 and 100 g, were divided into 4 groups of 40 animals each. According to the method described by Ingle and Higgins [10], rats, anesthetized with pentobarbital, were heminephroadrenalectomized on the right side by contralateral adrenal enucleation (ARH group). In the UNA group, one of three control groups, unilaterally nephroadrenalectomized rats were maintained on 1% saline. In the 1% NaCl group and the water group, sham-operated rats were maintained on 1% saline and tap water, respectively. Blood pressure and body weight were measured weekly. Of the 40 animals, 32 were sacrificed by decapitation, 8 each time at 2, 4, 6 and 8 weeks after operation, to measure CSs, renin activity (PRA), PRL and electrolytes in the plasma, and to weigh organs (the heart, kidneys, and adrenals). The remaining 8 rats were individually housed in KN650 metabolic cages (Natsume) for 8 weeks, to collect 24 h urine samples, in which urine volume and urinary electrolytes were measured, the data being presented as the mean of 3 daily data. All rats were maintained on solid laboratory food MF for rats (Oriental) containing 0.24% Na and 0.75% K, in an animal room kept at 22°C with a light cycle from 0800 h to 2200 h.

Plasma CSs concentrations

After extraction, 3 plasma MCs, corticosterone (Kendall’s compound B, B), deoxycorticosterone (DOC), and 18-hydroxy-deoxycorticosterone (18-OH-DOC), were separately determined by high performance liquid chromatography (HPLC). A 0.3 ml portion of the plasma sample, containing 300 μg of estrone as an internal standard, was extracted with 10 volumes of ethyl acetate. This organic layer was washed with 0.05 N NaOH solution and then distilled water. The solvent was then evaporated in N2 gas to dryness. The residue was dissolved in 20 μl of ethanol. Of the 20 μl solution, 5 μl was transferred with a microsyringe (Hamilton) to the HPLC column. A Shimadzu LC-2 HPLC was used with a Solute CN column, which was eluted with 50% methanol at a pressure of 40 kg/cm2. The eluant was monitored at UV 254 nm. Plasma CSs concentrations were calculated in terms of the peak area measured automatically with a Chromatopack C-RIA (Shimadzu). Of cold preparations of steroids, 18-OH-DOC, B, DOC, and estrone were obtained from Steraloids Corp., and 19-nor-DOC and 19-OH-DOC were donated by Dr. Gomez-Sanchez.

Measurements of PRA, plasma aldosterone, PRL, electrolytes in the blood and urine, and blood pressure

Bioassay as described by Skinner [11] was used with a modification to measure PRA. The coefficient of variation for this assay was 10.9%. To determine aldosterone, 0.5 ml of a plasma sample was extracted with 4 ml of dichloromethane. The radioimmunoassay (RIA) as described by Bayard et al. [12] was performed with the antibody obtained from CIS. The rate of extraction for this method was 85%. The detection limit was 3.0 pg/tube. The coefficients of variation for intra and inter-assay were 9.2 and 14.3%, respectively. Plasma PRL concentrations were determined by a double antibody technique with a RIA kit for rats obtained from NIAMDD with rat PRL labelled with 125I by the chloramine T method [13]. The detection limit was 1.0 ng of PRL. The coefficients of variation for intra and inter-assay were 12.0 and 8.0%, respectively.

Na and K in the blood and urine were measured by flame photometry. Systolic pressure was measured by the tail cuff method with an automatic manometer for rats (Ueda Kousan).

Statistical analysis

The results were presented in terms of the mean ± standard error. Student’s t-test was used to evaluate the significance of differences.

Results

Four weeks after operation, as shown in Fig. 4, blood pressure was 167.0±5.8 mmHg in the ARH group, 134.4±4.9 mmHg in the UNA group, 149.8±3.1 mmHg in the 1% NaCl group and 133.4±3.2 mmHg in the water group, the value for the ARH group being significantly higher than that for any other group (P<0.05). Despite the absence of a significant difference in body weight
among the four groups throughout the study period, in the ARH group, the blood pressure remained high thereafter, being 175.0 ± 13.2 mmHg at the 6th week and 176.0 ± 11.7 mmHg at the 8th week. In the ARH group, the heart and kidneys, as shown in Table 1, were significantly increased in weight 4 weeks after operation and thereafter. The weight of the adrenals showed a tendency to be greater in the UNA group than in the ARH group, but this difference was not significant. Neither the blood Na nor K concentration changed remarkably in any group.

The results of the metabolic studies are shown in Table 2. Among the three groups of animals receiving 1% saline, only in the ARH group were water intake and the volume of urine markedly increased with the increase in urinary excretion of Na 2 weeks after operation. There was not any noticeable change in water consumption, urine volume, or urinary Na or K excretion thereafter.

The urinary Na/K ratio had been as high as 3.9 ± 0.6 in the ARH group 2 weeks after operation, reflecting the increased Na excretion, but then suddenly changed and decreased to as low as 1.5 ± 0.2 by 4 weeks after operation, suggesting acceleration of sodium retention and potassium excretion. When a mixture of standard CSs was analyzed by the same HPLC, the peaks for all CSs studied separated distinctively: 18-OH-DOC (16.8), B (18.4), and DOC (26.0), in the increasing order of retention time (min) given in parentheses (Fig. 1). The mean recovery rate was 95.0 ± 4.5% with a mean reproducibility lower than 5%. The highest detection limit was 210 pg/tube. A calibration curve approximately passed the origin of the coordinate axes as shown in Fig. 2. The retention time (min) for 19-nor-DOC and 19-OH-DOC was 19.2 and 17.0, respectively. HPLC analyses of plasma samples taken from rats which received both adrenalectomy and testectomy confirmed that neither non-steroidal substances nor sex hormones in the plasma would not interfere with
Fig. 3. Typical chromatograms of corticosteroids extracted from plasma in adrenal regeneration hypertensive (ARH) rat and unilaterally nephroadrenalectomized (UNA) rat by HPLC at four weeks after operation.

Table 1. The changes in organs weights, plasma renin activity and plasma electrolytes (Na, K) in all experimental groups after treatment

<table>
<thead>
<tr>
<th>Groups and time after operation</th>
<th>Heart weight (mg/100g BW)</th>
<th>Kidney weight (mg/100g BW)</th>
<th>Adrenal weight (mg/100g BW)</th>
<th>PRA (ng/ml/h)</th>
<th>p-Na (mEq/l)</th>
<th>p-K (mEq/l)</th>
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<tr>
<td>ARH 2 W</td>
<td>289.3±8.4</td>
<td>311.8±26.1</td>
<td>6.1±1.5</td>
<td>4.8±0.5</td>
<td>139.5±0.5</td>
<td>3.7±0.1</td>
</tr>
<tr>
<td></td>
<td>324.6±13.6***</td>
<td>688.8±17.7***</td>
<td>8.3±1.8</td>
<td>3.0±0.8**</td>
<td>139.8±0.4</td>
<td>3.9±0.1</td>
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<tr>
<td></td>
<td>359.3±4.8*</td>
<td>657.4±22.7**</td>
<td>7.2±0.9</td>
<td>—</td>
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<td>—</td>
</tr>
<tr>
<td></td>
<td>371.2±5.5*</td>
<td>689.2±28.0***</td>
<td>6.3±0.5</td>
<td>5.5±0.7*</td>
<td>140.5±1.2</td>
<td>3.9±0.1</td>
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<tr>
<td>UNA 2 W</td>
<td>289.0±12.4</td>
<td>289.8±7.5</td>
<td>8.7±1.2</td>
<td>6.0±1.3</td>
<td>137.6±1.0</td>
<td>3.7±0.2</td>
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<tr>
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<td>290.6±5.7</td>
<td>602.8±34.7</td>
<td>9.1±2.1</td>
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<td></td>
<td>317.3±11.2</td>
<td>614.4±21.9</td>
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<td></td>
<td>324.6±13.6</td>
<td>601.8±11.6</td>
<td>7.6±1.5</td>
<td>6.0±0.3</td>
<td>138.5±1.0</td>
<td>3.5±0.1</td>
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<td>NaCl 2 W</td>
<td>267.7±12.3</td>
<td>377.4±5.2</td>
<td>5.7±0.3</td>
<td>7.1±0.8</td>
<td>139.8±0.5</td>
<td>3.9±0.1</td>
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<td></td>
<td>278.0±4.7</td>
<td>371.2±20.4</td>
<td>4.6±0.2</td>
<td>6.2±1.3</td>
<td>140.4±1.6</td>
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<tr>
<td></td>
<td>296.5±8.6</td>
<td>381.1±27.8</td>
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<tr>
<td></td>
<td>304.9±10.1</td>
<td>389.4±26.9</td>
<td>5.3±0.3</td>
<td>8.6±0.8</td>
<td>136.0±0.7</td>
<td>3.9±0.2</td>
</tr>
<tr>
<td>Water 2 W</td>
<td>230.2±4.4</td>
<td>336.4±8.3</td>
<td>5.1±0.4</td>
<td>14.3±1.3</td>
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<td>285.7±2.4</td>
<td>396.7±10.4</td>
<td>4.1±0.4</td>
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<td>304.9±10.1</td>
<td>353.3±3.2</td>
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<td>140.6±0.8</td>
<td>3.6±0.1</td>
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</table>

All values are the mean ± SEM. In all groups, n=8. Statistical analysis of ARH group and UNA group was done by Student's t-test. *, P<0.05; **, P<0.01; ***, P<0.001. BW=body weight.
CORTICOSTEROIDS AND PROLACTIN IN ARH RATS

FIG. 4. The changes in systolic blood pressure and body weight in all experimental groups before and after treatment, (●–●), ARH rats; (○–○), UNA rats; (▲–▲), sham-operated rats received 1% saline; (△–△), sham-operated rats received tap water. Each value represents the mean ± SEM. In all groups, n=8. Statistical analysis of the ARH group compared with other control groups was done by Student’s t-test.

* , P<0.05; **, P<0.01.

This analytical system. Typical chromatograms, shown in Fig. 3, showed peaks of CSs in the plasma samples from ARH and UNA rats 4 weeks after operation.

As shown in Table 1, the PRA levels in the ARH group were significantly lower than in any other group 4 weeks after operation and remained so thereafter.

Two weeks after operation, the plasma B concentration was 1.7±0.8 µg/dl in the ARH group, 25.8±5.4 µg/dl in the UNA group, 26.7±2.8 µg/dl in the 1% NaCl group, and 33.5±6.2 µg/dl in the water group, this level in the ARH group being significantly lower than that in any other group (P<0.01). These concentrations 4 weeks after operation were 15.9±1.1 µg/dl, 20.8±4.8 µg/dl, 18.5±2.2 µg/dl, 18.5±2.2 µg/dl, and 21.9±2.8 µg/dl, respectively, showing that the difference diminished. This plasma concentration in the ARH group recovered and approximated those in the other 3 groups 6 weeks after operation and thereafter (Fig. 5).

The plasma aldosterone concentration 2 weeks after operation was 3.9±0.6 ng/dl in the ARH group, 12.4±1.4 ng/dl in the UNA group, and 15.9±1.9 ng/dl in the 1% NaCl group. These concentrations being significantly lower than the concentration of 28.1±3.1 ng/dl in the water group (P<0.001, P<0.01, and P<0.001, respectively). This plasma aldosterone concentration in the ARH group was also significantly lower than that in the UNA group (P<0.001). Even 4 weeks after operation, the aldosterone concentration was 7.0±0.2 ng/dl in the ARH group, 11.1±1.4 ng/dl in the UNA group, 15.9±2.5 ng/dl in the 1% NaCl group, and 24.5±5.1 ng/dl in the water group, showing the same tendency as in data obtained 2 weeks after operation, the concentration in the ARH group also being significantly lower than that in the UNA group (P<0.01). Even 4 weeks after operation, the aldosterone concentration was 7.0±0.2 ng/dl in the ARH group, 11.1±1.4 ng/dl in the UNA group, 15.9±2.5 ng/dl in the 1% NaCl group, and 24.5±5.1 ng/dl in the water group, showing the same tendency as in data obtained 2 weeks after operation, the concentration in the ARH group also being significantly lower than that in the UNA group (P<0.01). The aldosterone concentration 2 weeks after operation was 3.9±0.6 ng/dl in the ARH group, 12.4±1.4 ng/dl in the UNA group, and 15.9±1.9 ng/dl in the 1% NaCl group. These concentrations being significantly lower than the concentration of 28.1±3.1 ng/dl in the water group (P<0.001, P<0.01, and P<0.001, respectively). This plasma aldosterone concentration in the ARH group was also significantly lower than that in the UNA group (P<0.001). Even 4 weeks after operation, the aldosterone concentration was 7.0±0.2 ng/dl in the ARH group, 11.1±1.4 ng/dl in the UNA group, 15.9±2.5 ng/dl in the 1% NaCl group, and 24.5±5.1 ng/dl in the water group, showing the same tendency as in data obtained 2 weeks after operation, the concentration in the ARH group also being significantly lower than that in the UNA group (P<0.01). The concentrations 6 and 8 weeks after operation were 15.1±0.5 and 17.8±0.6 ng/dl, respectively, in the ARH group, 13.0±0.5 and 14.8±0.4 ng/dl in the UNA group, 14.9±0.5 and 18.2±1.4 ng/dl in the 1% NaCl group, and 24.3±1.2 and 20.5±1.8 ng/dl in the water group, the suppression being significant even after 6 weeks in all groups except for the water group (P<0.01), whereas there was not any significant difference among the four groups 8 weeks after operation (Fig. 6).

The plasma DOC concentrations in the ARH, UNA, 1% NaCl, and water groups were 0.23±0.11, 0.42±0.10, 0.33±0.12, and 0.21±0.10 µg/dl, respectively, 2 weeks after operation, and 0.60±0.14, 0.32±0.10, 0.34±0.10, and 0.52±0.13 µg/dl 4 weeks after operation. Although there was not any difference in the DOC concentration between the ARH group and any other group 2 weeks after operation, the concentration in the ARH group was 1.2 to 2 times higher than those in the other groups 4 weeks after operation. The concentrations in the four groups were essentially
Fig. 5. The changes in plasma corticosterone levels in all experimental groups after treatment. ■, ARH rats; □, UNA rats; ▲, sham-operated rats received 1% saline; ▣, sham-operated rats received tap water. Each value is the mean±SEM. In all groups, n=8. Statistical analysis of the ARH group compared with other control groups was done by Student’s t-test. *, P<0.01.

Fig. 6. The changes in plasma aldosterone levels in all experimental groups after treatment. Each value is the mean±SEM. In all groups, n=8. Symbols and statistical analysis are the same as in Fig. 5. *, P<0.05; **, P<0.01; ***, P<0.001.

The plasma 18-OH-DOC concentrations in the ARH, UNA, 1% NaCl, and water groups were 1.2±0.4, 5.3±0.5, 5.0±0.5, and 4.7±1.2 μg/dl, respectively, 2 weeks after operation, this concentration in the ARH group being significantly lower than that in any other group (P<0.001). Then, like DOC, 4 weeks after operation, the plasma 18-OH-DOC concentration rose markedly in the ARH
group to 7.0±0.9 μg/dl, this concentration being significantly higher than those of 4.0±1.0 μg/dl in the UNA group, 3.5±0.6 μg/dl in the 1% NaCl group, and 3.1±1.3 μg/dl in the water group (P<0.01). There was not any significant difference in the concentration among the four groups 6 or 8 weeks after operation (Fig. 8). In addition, there were more peaks than one between B and DOC, but their presence was not specific to the ARH group. Neither 19-OH-DOC nor 19-nor-DOC was identified.

Four weeks after operation, the plasma PRL concentration was 4.6±0.8 ng/ml in the ARH group. This concentration was significantly lower
than the 8.1±1.9 ng/ml concentration in the UNA group, 7.9±1.2 ng/ml in the 1% NaCl group, and 8.2±1.0 ng/ml in the water group (P<0.01). There was not any significant difference in plasma PRL concentration among the four groups 2, 6 or 8 weeks after operation (Fig. 9).

**Discussion**

The view that excessive secretion of CSs, in particular those having MC activity, from the regenerated adrenal is responsible for the development and persistence of ARH has been proposed. This view is based on several observations including the prevention of the development of ARH by removal of the hypophysis [14],
hypotensive effects of MC antagonists such as spironolactone [15] and its derivatives [16], low levels of PRA in ARH [17], and a decreased K concentration in the muscle despite there being a normal K concentration in the serum [18]. Kenyon et al. [19] have stated that exchangeable body sodium increases in ARH, just as in hypertension due to DOC. In the present series of experiments, the Na/K ratio was high 2 weeks after operation probably due to adrenal insufficiency and salt appetite, but low 4 weeks after operation, suggesting an abrupt enhancement of MC activity between these two measurements.

In the ARH group, plasma concentration time curves for both DOC and 18-OH-DOC were parallel throughout the study period except for 2 weeks after operation. That is these concentrations in the ARH group were quite high 4 weeks after operation, but 6 and 8 weeks after operation, fell to levels similar to those in the other 3 groups. This pattern is consistent with changes in the urinary Na/K ratio as described above. Consequently, it is possible that this enhanced secretion of DOC and 18-OH-DOC may have participated in increasing rising blood pressure in the ARH group at between 2 and 4 weeks, but other factors may account for hypertension after the 4th week e.g. a metacorticoid state of hypertension [20]. A comparison of CSs concentrations among groups showed that neither nephrectomy nor the ingestion of saline affected plasma concentrations of CSs other than aldosterone.

It was reported as early as the 1930s that DOC causes hypertension. DOCA, an acetate ester of DOC, was used to produce a pathological model of hypertension. In order to produce hypertension with certainty, large doses of DOCA were often used. Increasing intrinsic DOC, metyrapone, an 11-β-hydroxylase inhibitor, can also be used to induce hypertension in animals [21]. Hypertension in these animal models is hypervolemic secondary to sodium retention at least early after the onset, often leading to hypokalemia. In ARH, however, as in our results shown above, the serum K concentration has been reported to be not significantly different from that in control animals. The reason for this is unknown, but may represent the achievement of a severer effect by pharmacological blood levels of DOC [22]. There were also studies in which a decrease in the K concentration in muscle was observed in ARH. Consequently, the participation of DOC in ARH cannot be denied. The precise mechanism of DOCA-salt hypertension is still disputed, but it has been estimated that DOC can exert its action directly on the vascular smooth muscles [23]. Thus, DOC may be a factor which plays a role in the process of development of malignant hypertension as a result of advanced cardiovascular diseases, a process often encountered in ARH.

Being only 1.3% as active as aldosterone in its capacity to bind to receptors in the kidneys, 18-OH-DOC has been considered to be one of the very important MCs because its secretion from the adrenals is several times and several hundreds times greater than the secretion of DOC and aldosterone, respectively [24]. Nicholls et al. [25] stated that 18-OH-DOC was only 0.1% as active as aldosterone in terms of sodium retention activity and induced only a little potassium diuresis. Carroll et al. [26] reported that repeated administration of 18-OH-DOC for a relatively long period raised the blood pressure without changing the electrolyte status. A review of literature on DOC and 18-OH-DOC in ARH revealed that an increase in DOC early in the course of adrenal regeneration is followed by an increase in 18-OH-DOC 4 weeks after operation and thereafter. In the present study, however, both DOC and 18-OH-DOC were increased 4 weeks after operation. This may be explained by the fact that the increased secretion of ACTH, in response to insufficient production of CSs until the 2 nd week of ARH, increased CSs production in the regenerated adrenals, but 11-β-hydroxylase activity remained suppressed until the 4th week of ARH allowing increased production of CSs only up to the level of DOC. This may lead to an increase in the production of its by-product 18-OH-DOC. Different methods used in different studies, especially analytical techniques to determine CSs and differences in the strain and age of the rats used, may account for such difference in results as those described above.

Since Gomez-Sanchez et al. [27] chemically identified 19-nor-DOC after its isolation from the urine of ARH rats, this steroid and compounds relative to it have been extensively studied. In ARH rats, however, this steroid could not have been demonstrated in either peripheral blood [28] or blood taken from the adrenal veins [29], nor was it detected by HPLC in any blood sample in
this study. Its absence from the blood, despite its presence in the urine, has been considered to be due to peripheral transformation to 19-nor-DOG from its precursors such as 19-OH-DOG, 19-oxo-DOC, and 19-oic-DOG [30]. However, none of the serum samples taken from ARH rats at different times during the study period showed any particular peak compared with those taken from rats of the other groups.

Recently, it has been shown that the secretion of aldosterone is controlled by the inhibitory action of DA in animals of various species including rats and man. An in vivo experiment demonstrated a fall in the blood aldosterone concentration after the administration of dopaminergic drugs such as CB-154, and a rise after the administration of metoclopramide (MCP), an antagonist of central and peripheral DA receptors [31, 32]. Although the secretion of aldosterone is altered mainly with ACTH, angiotensin II and K, none of them has been considered to be involved in this rise due to MCP [33, 34]. There has been no consistent view in regard to whether this inhibition of intrinsic DA is mediated by the special adrenocortical receptors. However, Sowers et al. [35] estimated the involvement of the inhibition of 18-hydroxylase at a late step in aldosterone synthesis. In the present study, the plasma PRL concentration was measured as an index to represent the central DA activity. The index showed a fall 4 weeks after operation, indicating enhanced DA activity, but the mechanism of this phenomenon has not yet been clarified by our experiments. The data concerning the brain catecholamine in DOCA-salt hypertensive rats are still controversial [36, 37]. According to a recent report by Huang et al. [38], in sheep, the administration of DA in the cerebral ventricle, in a smaller dose than that used in any previous studies resulted in a drop in the blood aldosterone concentration and a rise in the PRA level, whereas an intraventricular dose of MCP led to a rise in the blood aldosterone concentration and a fall in the PRA level. Neither DA nor MCP produced any change in the blood aldosterone concentration or PRA when injected intravenously at the same smaller dose. An intraventricular dose of either substance failed to cause any change in blood pressure, cerebral pressure, Na, K or cortisol. The case was the same with denervated sheep which had received autotransplantation of pieces of adrenal tissue. This inhibitory regulation of aldosterone secretion by central DA was consequently estimated to be not mediated by blood DA or the autonomic nervous system. The rise in the PRA level may have been secondary and mediated by an antidiuretic hormone. Because DA injected into the cerebral ventricle did not affect the secretion of ACTH there must be a hypophysal factor other than that to regulate the secretion of aldosterone. Peptides such as α-melanocortin, β-lipotropin and β-melanotropin arising from proopiomelanocortin have been estimated to be the hypophysal factor. Incidentally, in rats, an alternative pathway where aldosterone is synthesized from DOC via 18-OH-DOC is known [39]. In addition to inhibition of the renin-angiotensin system due to sodium retention, the increased activity of central DA described by Huang et al. or that observed in the present study may be partially responsible for such a decrease in the secretion of aldosterone despite overproduction of DOC and 18-OH-DOC 4 weeks after operation.

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References


