Aldosterone Infusion into the Rat and Dose-Dependent Changes in Blood Pressure and Arterial Ionic Transport

ELLEN T. GARWITZ, B.A., AND ALLAN W. JONES, PH.D.

SUMMARY Induction of hypertension by implantation or injection of deoxycorticosterone acetate (DOCA) requires a dose well above the physiological range. The objective of this study was to produce hypertension in rats by chronic infusion of d-aldosterone, a more potent mineralocorticoid. Aldosterone infused at a dose of 1 μg/hr for 4 weeks gave a maximal rise in systolic blood pressure (132 ± 3 vs 203 ± 7 mm Hg). A significant rise in blood pressure was achieved at 0.1 ng/hr (170 ± 6 mm Hg) which was associated with a 2.3-fold rise in plasma aldosterone levels (7.6 ± 0.4 vs 17.7 ± 2.2 ng/dl). A series of isotope flux studies on the aorta and femoral artery from hypertensive animals demonstrated increases in "K and "Cl turnover. In both vessels the largest changes in ion turnover were observed in vessels from animals infused with aldosterone at 0.25 μg/hr. Increases in "K and "Cl turnover were detected as early as 1 week after the start of aldosterone infusion, well before a significant rise in blood pressure had occurred. (Hypertension 4: 374-381, 1982)

KEY WORDS • aldosterone • vascular smooth muscle • ion transport • radioisotopes

SINCE its discovery by Conn and Louis1 in 1955, primary aldosteronism has been considered a causative factor in at least some hypertensive patients. Experimentally, mineralocorticoid excess combined with high salt intake and reduced renal mass has been shown to cause hypertension in at least some species of animals, mainly, in the rat and young pig. DOCA salt treatment, particularly in the rat, has therefore become a well-established model of mineralocorticoid hypertension. In the majority of clinical cases, however, mineralocorticoid-related hypertension is due to an excess of aldosterone and not DOCA.2 Hypersecretion of DOCA is rarely observed clinically except in unusual cases of congenital adrenal-cortical enzymatic deficiencies. Moreover, induction of mineralocorticoid hypertension in experimental animals requires administration of DOCA in pharmacological doses. For example, Grekin et al.3 reported that during 40 days of DOCA administration to young pigs, plasma DOCA levels remain elevated at least 10 fold over preimplantation levels, well above physiological levels.

It has been observed clinically that a significant number of essential hypertensive patients are found to have plasma aldosterone levels that are only moderately elevated.4 It would therefore be appropriate to examine the effects of moderate doses of aldosterone that produce plasma levels similar to those observed in many hypertensive patients. Despite one early report,5 it was anticipated on the basis of more recent work that the hypertensinogenic potency of aldosterone in the rat is equal to or superior to DOCA.6,7 A primary objective of the present study was to examine in the rat the relationship between plasma levels of aldosterone and the development of hypertension at doses of aldosterone within the "stressed" physiological range.

The pathogenic mechanisms responsible for the development of steroid induced hypertension have not been clearly defined. Fundamental alterations in the function of vascular smooth muscle have been considered to play a significant role. Hinke8 first demonstrated that tail arteries from DOCA hypertensive rats maintain a greater degree of KCl-induced contracture in low calcium solutions than arteries from normotensive animals. In a similar manner, Holloway and Bohr9 reported that a significantly higher level of external calcium was required to inhibit a KCl-induced contracture in femoral arteries from DOCA hypertensive animals compared to arteries from control animals. These findings indicate a decreased

From the Department of Physiology, University of Missouri, Columbia, Missouri. Supported by United States Public Health Service Grant HL-15852.

Address for reprints: Ellen T. Garwitz, Department of Physiology, University of Missouri, Columbia, Missouri 65212.

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ability of calcium to stabilize vascular smooth muscle membrane in vessels from DOCA hypertensive animals. Previous reports from our laboratory\textsuperscript{10, 11} and others\textsuperscript{18} have indicated increases in passive membrane permeability to Na, K, and Cl in vessels from DOCA hypertensive animals. These alterations in electrolyte metabolism also precede the onset of elevated blood pressure and reflect a decreased ability of calcium to stabilize the membrane.\textsuperscript{19} Our present study reaffirms the findings of altered electrolyte metabolism in steroid hypertension induced by the chronic infusion of aldosterone. Preliminary reports of this work have been published in abstract form.\textsuperscript{18, 14}

Methods

Animals and Tissues

The left kidney was removed from anesthetized male Sprague Dawley rats weighing 150 to 200 gs. An osmotic minipump (ALZET) containing d-aldosterone (SIGMA) dissolved in polyethylene glycol was implanted subcutaneously in the treated animals. Rats in the control group received a pump containing the vehicle only. The control animals were given a 1% wt/vol NaCl solution as drinking fluid. Treated animals were given a supplement of KCl (0.3% wt/vol) in the NaCl solution to maintain body weight. All animals received a diet of normal rat chow and were weighed weekly. Saline intake was measured as the 24-hour removal from calibrated drinking bottles. Systolic blood pressure was determined weekly by a tail-cuff method.

The morning of the experiment the animals were decapitated and bled into chilled tubes containing di-sodium ethylenediaminetetraacetate (EDTA). Blood samples were then centrifuged in the cold to obtain plasma for aldosterone assay. Plasma aldosterone concentration was then determined by radioimmunoassay using the method of Buhler et al.\textsuperscript{14} The thoracic aorta and femoral arteries were removed and placed in a K-free dissection solution containing 0.25 mM Ca\textsuperscript{2+}. Loose connective tissue was removed from the vessels, which were then slit lengthwise and mounted on stainless steel holders. The length of the aortic strip was measured, and the wet weight of the tissue determined to obtain a weight (mg) to length (cm) ratio. The adrenal gland, spleen, heart, and intact kidney were also removed from the animals and weighed.

Solutions

The normal physiological solution used had the following millimolar composition: Na\textsuperscript{+}, 146.2; K\textsuperscript{+}, 5.0; Mg\textsuperscript{2+}, 1.2; Ca\textsuperscript{2+}, 2.5; Cl\textsuperscript{-}, 143.9; HCO\textsubscript{3}{-}, 13.5; H\textsubscript{2}PO\textsubscript{4}{-}, 1.2 and glucose, 11.44. Solutions were gassed with 97% O\textsubscript{2} - 3% CO\textsubscript{2} mixture at 37°C to obtain a pH of 7.4.

Extracellular Space and Electrolytes

Aortic and femoral artery strips were incubated at 37°C in physiological solution followed by a 15-minute incubation in a similar solution containing labelled \textsuperscript{86}CoEDTA (0.5 μCi/ml) and non-labelled CoEDTA (2mM).\textsuperscript{14} The vessels were then lightly blotted and placed in plastic vials for weighing. Water contents were determined by the difference in weight after oven drying (20 hours at 93°C). The dry specimens were counted in a gamma counter, and the \textsuperscript{86}CoEDTA space was determined from the ratio of counts/sec in the strip to counts/sec in a weighed sample of the incubation medium. The extracellular space was calculated as kg H\textsubscript{2}O/kg dry wt. “Cell water” was estimated as the difference between total water and the \textsuperscript{86}CoEDTA space.

Tissues undergoing electrolyte analysis were ashed at 90°C in H\textsubscript{2}O\textsubscript{2} (30% wt/vol) containing AgNO\textsubscript{3} to precipitate Cl\textsuperscript{-}. The ash was dissolved in a solution containing 0.1 N HNO\textsubscript{3}, 10 mM La\textsuperscript{3+}, and 15 mM LiNO\textsubscript{3}. Mg, Ca, and Ag were analyzed with an atomic absorption spectrometer, and Na and K with a flame photometer. Chloride content was calculated from the difference between total Ag added and final Ag in the extract.\textsuperscript{14} Cellular electrolyte contents were estimated as the difference between total electrolyte content and that dissolved in the \textsuperscript{86}CoEDTA space. Electrolyte contents were expressed as mmoles/kg dry wt.

Isotope Techniques

These procedures have been employed and described in detail previously.\textsuperscript{17, 18} The vessels were equilibrated at 37°C in normal physiological salt solution containing \textsuperscript{42}K and \textsuperscript{36}Cl for 3 hours. After a 1–2 second rinse, the strips were then passed through a series of tubes containing nonradioactive solution. The activity in the tubes and the vessels was counted on a liquid scintillation counter. Washout curves were calculated by sequentially adding the tissue and the tube counts in reverse order. These counts were then normalized in terms of percent initial activity. A digital computer was used to process the data. The fraction exchanged per minute for each washout period was computed, which under steady-state conditions represents the rate constant (k, min\textsuperscript{-1}). The washout experiments were performed at 37°C. At this temperature, the \textsuperscript{42}K and \textsuperscript{36}Cl efflux curves can be easily separated into fast and slowly exchanging components. For \textsuperscript{42}K, the rate constants between 20 and 40 minutes were averaged to obtain an estimate of cellular K turnover. Cellular Cl turnover was estimated as described previously.\textsuperscript{17} Turnover (k = 1/t) was calculated from the time required for the initial counts remaining after 1 minute washout to fall to 1/e. This approach yields an accurate description of a component following a single homogeneous exponential or as a statistically distributed component.

The ED\textsubscript{50}'s for the effect of aldosterone infusion on \textsuperscript{42}K and \textsuperscript{36}Cl turnover were calculated as follows. The basal \textsuperscript{42}K turnover in animals infused with the vehicle was subtracted from the rate observed in vessels from aldosterone treated animals to obtain Δ k\textsubscript{max}. The ED\textsubscript{50} was determined by linear interpolation of the infusion rate required to produce a 50% maximal rise in \textsuperscript{42}K or \textsuperscript{36}Cl turnover.
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Statistical Methods

The Student's t test was used when one experimental group was compared to the control group. For simultaneous multiple comparisons (each of the five experimental groups compared to the control), the Bonferroni Method was utilized as described by Wallenstein et al. One-way analysis of variance was first performed and then a modified test statistic was calculated as:

\[ t = \frac{\bar{x}_i - \bar{x}_j}{s \sqrt{\frac{1}{n_i} + \frac{1}{n_j}}} \]

where \( s^2 \) is the mean square within groups from the analysis of variance (ANOVA) table. This test statistic was compared to a conservative critical value generated using the Bonferroni method at an overall \( p \) level of 0.025. This method was chosen as the most appropriate test for making simultaneous multiple comparisons of a preplanned nature.

Results

The time course for the development of hypertension in rats infused with aldosterone is shown in figure 1. Systolic blood pressure in rats infused with aldosterone at 0.05 \( \mu \)g/hr did not differ from rats infused only with the vehicle over the 4-week period. At higher infusions (0.1 - 1.0 \( \mu \)g/hr) a significant rise in systolic blood pressure was evident after 2 weeks of aldosterone infusion. The rate of hypertension development was similar at infusions in the 0.1 to 1.0 \( \mu \)g/hr range. An infusion of 0.25 \( \mu \)g/hr appeared to be optimal for the rapid development of hypertension. At higher infusions, the rate of hypertension development was not enhanced, but followed a similar time course to that observed in rats infused with aldosterone at 0.25 \( \mu \)g/hr.

The systolic blood pressure and plasma aldosterone levels in rats infused with aldosterone for 4 weeks are shown in figure 2. A 2.3-fold increase in plasma aldosterone (7.6 ± 0.9 vs 17.7 ± 2.2 ng/dl) was associated with a significant elevation in blood pressure (133 ± 3 vs 171 ± 6 mm Hg). Blood pressure responses appeared to plateau at an infusion rate of 0.25 \( \mu \)g/hr, whereas plasma levels of aldosterone peaked at 0.5 \( \mu \)g/hr. As shown in figure 2, plasma aldosterone levels in rats infused at 0.5 and 1.0 \( \mu \)g/hr displayed considerable scatter. This variability may in part be due to animal differences in the metabolic clearance of aldosterone at high rates of infusion.

Some general characteristics of aldosterone-infused rats are summarized in table 1. After 4 weeks of treatment, aldosterone-infused animals generally displayed lower body weight and elevated consumption of saline. Comparison of organ weights (normalized to body weight) indicated hypertrophy of both cardiac and
Table 1. General Characteristics of Aldosterone-Infused Rats after 4 Weeks of Treatment

<table>
<thead>
<tr>
<th>Aldosterone infusion rate (µg/hr)</th>
<th>Plasma aldosterone (ng/dl)</th>
<th>Systolic blood pressure (mm Hg)</th>
<th>Saline intake (ml/day)</th>
<th>Body weight (g)</th>
<th>Heart/body (mg/g)</th>
<th>Kidney/body (mg/g)</th>
<th>Adrenal/body (mg/g X 10^-2)</th>
<th>Splenic/body (mg/g)</th>
<th>Aortic wt/length (mg/cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O (vehicle)</td>
<td>(11)</td>
<td>7.6</td>
<td>± 0.88</td>
<td>133</td>
<td>84</td>
<td>323</td>
<td>3.07</td>
<td>6.6</td>
<td>8.4</td>
</tr>
<tr>
<td>0.05</td>
<td>(12)</td>
<td>12.8</td>
<td>± 0.84</td>
<td>131</td>
<td>91</td>
<td>348</td>
<td>3.25</td>
<td>7.3</td>
<td>9.1</td>
</tr>
<tr>
<td>0.10</td>
<td>(9)</td>
<td>17.7</td>
<td>± 2.2</td>
<td>171*</td>
<td>120</td>
<td>319</td>
<td>3.53</td>
<td>8.3*</td>
<td>9.3</td>
</tr>
<tr>
<td>0.25</td>
<td>(13)</td>
<td>32.5*</td>
<td>± 3.3</td>
<td>194*</td>
<td>139</td>
<td>254*</td>
<td>4.18*</td>
<td>10.9*</td>
<td>11.2</td>
</tr>
<tr>
<td>0.50</td>
<td>(7)</td>
<td>58.3*</td>
<td>± 9</td>
<td>197*</td>
<td>175*</td>
<td>227*</td>
<td>3.92*</td>
<td>12.2*</td>
<td>10.2</td>
</tr>
<tr>
<td>1.00</td>
<td>(9)</td>
<td>58.3*</td>
<td>± 7</td>
<td>202*</td>
<td>174*</td>
<td>196</td>
<td>3.87*</td>
<td>12.9*</td>
<td>12.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>± 7</td>
<td>± 7</td>
<td>± 70</td>
<td>± 11</td>
<td>± 17</td>
<td>± 0.5</td>
<td>± 1.4</td>
</tr>
<tr>
<td>*</td>
<td></td>
<td></td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>ANOVA F</td>
<td>29.89</td>
<td>40.83</td>
<td>6.18</td>
<td>24.92</td>
<td>9.94</td>
<td>28.68</td>
<td>4.38</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Significant differences were found by comparison to the vehicle-infused animals, at p < 0.025 using Bonferroni method for simultaneous multiple comparisons. For each parameter, each experimental group was compared to the control animals infused with the vehicle only.

Numbers of animals are in parenthesis. Values are means ± standard error of mean; NS = not significant.

Aldosterone-induced hypertension in renal tissues from hypertensive animals. A trend toward increases in aortic weight to length ratios in hypertensives was also apparent. However, a statistically significant elevation was observed only in animals infused with aldosterone at 0.25 µg/hr. The general health of the animals infused at this rate was consistently better than the health of animals infused at higher rates, as shown by the higher body weight. This in part may explain the greater extent of aortic hypertrophy in animals infused at 0.25 µg/hr. No significant alterations in the weights of the adrenal gland and spleen from hypertensive animals were detected. Cardiac hypertrophy is expected in light of the chronic increase in afterload presented to the left ventricle in hypertensive animals. Hypertrophy of the remaining kidney has been previously reported in steroid-induced hypertensive animals and has been attributed to tubular hyperplasia, hypertrophy, and dilation resulting from the high salt intake and persistent hypokalemia.

The water and electrolyte contents of aortas and femoral arteries from vehicle-infused and 0.25 µg/hr aldosterone-infused animals are compared at the bottom of table 2. Cell water in expressed in terms of tissue dry weights. When expressed in terms of cell water, no significant differences in cell K concentrations were observed (e.g., vehicle, 140 ± 9 mmoles/kg cell H2O, and 0.5 µg/hr, 154 ± 5 mmoles/kg cell H2O). The water and electrolyte contents of femoral arteries from vehicle-infused and 0.25 µg/hr aldosterone-infused animals are compared at the bottom of table 2. Cell water was slightly elevated in femoral arteries from hypertensive animals, but this was not statistically significant. The elevations were statistically significant for total Na and Mg contents as well as Na, Mg, and K contents corrected for the extracellular space. The elevation in corrected Mg and K levels may represent some degree of cellular hypertrophy in vessels from hypertensive animals, whereas
TABLE 2. Water and Electrolyte Distribution in Aortas and Femoral Arteries from Rats Infused with Vehicle and Aldosterone

<table>
<thead>
<tr>
<th>Infusion rate (μg/hr)</th>
<th>Water (kg H₂O/kg dry wt)</th>
<th>Total electrolyte (m mole/kg dry wt)</th>
<th>Total - ⁶⁷CoEDTA (m mole/kg dry wt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artery</td>
<td>Total ⁶⁷CoEDTA Cell</td>
<td>Na K Cl Ca Mg</td>
<td>Na K Cl Ca Mg</td>
</tr>
<tr>
<td>Aorta</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2.33 ± 0.07</td>
<td>0.79</td>
<td>300 ± 15 336 ± 13.4 ± 9 115 ± 4 18 ± 0.5 ± 0.4</td>
</tr>
<tr>
<td>(vehicle)</td>
<td></td>
<td></td>
<td>9.9 ± 0.4 ± 0.4 4 ± 1 ± 7 ± 0.5 ± 0.4</td>
</tr>
<tr>
<td>(9 rats)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.05</td>
<td>2.33 ± 0.14</td>
<td>0.91</td>
<td>277 ± 123 328 ± 16.6 ± 8 13 ± 2.3 ± 0.3</td>
</tr>
<tr>
<td>(7 rats)</td>
<td></td>
<td></td>
<td>10.5 ± 6 3 ± 17 ± 2.2 ± 0.3</td>
</tr>
<tr>
<td>0.10</td>
<td>2.25 ± 0.13</td>
<td>0.92</td>
<td>289 ± 128 328 ± 13.7 ± 6 9 ± 0.7 ± 0.2</td>
</tr>
<tr>
<td>(8 rats)</td>
<td></td>
<td></td>
<td>10.6 ± 5 ± 3 ± 11 ± 0.7 ± 0.2</td>
</tr>
<tr>
<td>0.25</td>
<td>2.51 ± 0.31</td>
<td>1.06*</td>
<td>310 ± 165* 345 ± 15.8 ± 8 18 ± 0.5 ± 0.5</td>
</tr>
<tr>
<td>(8 rats)</td>
<td></td>
<td></td>
<td>13.3 ± 4 ± 8 ± 13 ± 0.6 ± 0.5</td>
</tr>
<tr>
<td>0.50</td>
<td>2.23 ± 0.13</td>
<td>0.91</td>
<td>281 ± 145* 322 ± 15.1 ± 9 ± 14 ± 0.8 ± 0.5</td>
</tr>
<tr>
<td>(9 rats)</td>
<td></td>
<td></td>
<td>11.5 ± 12 ± 6 ± 12 ± 0.8 ± 0.5</td>
</tr>
<tr>
<td>1.00</td>
<td>2.23 ± 0.13</td>
<td>0.86</td>
<td>276 ± 135 296 ± 14.8 ± 6 ± 12 ± 13 ± 1.0 ± 0.8</td>
</tr>
<tr>
<td>(5 rats)</td>
<td></td>
<td></td>
<td>10.3 ± 3 ± 6 ± 12 ± 16 ± 1.1 ± 0.8</td>
</tr>
</tbody>
</table>

ANOVA

*F  NS NS 4.25 NS 9.54 NS NS NS NS 9.38 NS NS NS NS

Values are means ± standard error of mean; NS = not significant.

*For aortas, represents significant difference from vehicle-infused animals at p < 0.025 using Bonferroni method for simultaneous multiple comparisons.

*For femoral arteries, represents significant difference from vehicle at p < 0.05; tp < 0.01, using Student’s t test.

increased Na contents represent large contributions from extracellular adsorption sites as well as that dissolved in cell water.

Previous work from our laboratory has indicated that marked increases in ⁴¹K and ³⁵Cl turnover are associated with DOCA-salt hypertension in rats.⁴¹ Similar changes were observed in ⁴¹K turnover in aortas and femoral arteries from aldosterone-infused animals and are presented in figure 3. The largest increases in ⁴¹K turnover for both tissues were observed at an infusion of 0.25 μg/hr. Control rats infused with the vehicle had a slightly higher basal ⁴¹K turnover than control animals not receiving the vehicle, but this was not statistically significant. The consistent increase in K turnover in vessels from aldosterone-infused hypertensive rats was not associated with a change in cellular K concentrations. Estimates of cellular K concentrations obtained by extrapolation from the efflux curves to time equal zero did not indicate significant alterations in the cellular K pool in vessels from hypertensives (aorta vehicle: n = 11, 140 ± 6 mmol/kg cell H₂O vs 0.25 μg/hr, n = 8, 139 ± 7 mmol/kg cell H₂O). This suggests that increases in passive effluxes of K are compensated by an increase in active inward K transport.

Significant elevations in ³⁵Cl turnover in aortas and femoral arteries were observed at infusions of 0.1 μg/hr and above (fig. 4). Infusion of the vehicle did significantly elevate basal ³⁵Cl turnover in the aorta compared to control rats not receiving the vehicle but did not in the femoral artery. This effect was unexpected and cannot readily be explained. The ED₅₀'s for both ⁴¹K and ³⁵Cl were quite similar in each of the two vessels. Slowly exchanging chloride contents estimated from the efflux curves were not significantly altered by aldosterone treatment (aorta-vehicle; n = 10), 63 ± 7 mmol/kg cell H₂O vs 0.25 μg/hr (n = 8), 60 ± 8 mmol/kg cell H₂O.

To determine whether these alterations in ion transport precede the onset of elevated blood pressure, rats were infused at 0.25 μg/hr for 1 week. Systolic blood pressure in these animals was not significantly different from that in vehicle-infused animals (132 ± 6 vs 133 ± 3 mm Hg). ⁴¹K and ³⁵Cl turnover in the aorta was, however, significantly elevated after aldosterone infusion of 1 week. The rate constants for ⁴¹K were (n = 8) 0.0125 ± 0.001 vs (n = 13), 0.0095 ± 0.0005; and for ³⁵Cl (n = 7), 0.234 ± 0.011 vs (n = 13), 0.191 ± 0.009 min⁻¹, in the aldosterone and vehicle groups, respectively.
Discussion

A continuous chronic infusion of aldosterone coupled with high salt intake and reduced renal mass leads to the development of hypertension in the rat. Hypertension can be produced by the administration of aldosterone doses that produce plasma levels no greater than those that can be achieved endogenously in response to stress. The plasma aldosterone levels both in control and hypertensive rats reported in our study are comparable to those previously reported by others in experimentally induced high aldosterone states. Freeman et al. reported plasma aldosterone levels of 37.9 ± 8.0 ng/dl in rats made hypertensive by a 5-day constant infusion of ACTH, compared to 8.7 ± 1.4 ng/dl in their control animals. Plasma aldosterone levels in renal hypertensive rats (two-kidney, one clip) reported by the same group were 19.5 ± 5.5 ng/dl in 5-week hypertensive animals and 54.0 ± 28.5 ng/dl for 10-week hypertensive rats compared to 11.6 ± 1.4 ng/dl in control animals. In these two studies, the radioimmunoassay procedure utilized was identical to the assay used in our study. Chronic sodium depletion in rats has also been shown to elevate plasma aldosterone levels to very high values. After 5 days on a sodium deficient diet, Campbell et al. reported plasma aldosterone levels of 74 ± 6 ng/dl compared to 2.4 ± 0.3 ng/dl in rats on a normal sodium intake. Clearly, the range of plasma aldosterone levels achieved by the chronic administration of aldosterone in our study (17-60 ng/dl) is well within the "stressed" physiological range.

The pathogenic mechanisms responsible for the development of mineralocorticoid induced hypertension have not been clearly defined. Alterations in the permeability characteristics of the vascular smooth muscle membrane may be a critical factor in the etiology of this disease. The increases in K and Cl turnover observed in the present study are similar to those induced by exposure to a number of vasoactive agents. Therefore, the observed changes in vascular smooth muscle ion turnover during mineralocorticoid hypertension may represent a shift toward a state of sustained contraction and increased total peripheral resistance. Jones and Hart reported that, in DOCA hypertensive animals, alterations in membrane ion turnover precede the onset of elevated blood pressure. We have observed similar alterations in ion turnover as early as 1 week after the start of aldosterone infusion in aldosterone-induced hypertensive rats. This suggests that alterations in vascular smooth muscle ion turnover are an important factor in both the onset and maintenance of mineralocorticoid induced hypertension.
There is also evidence that central nervous system mechanisms may be involved in the pathogenesis of experimental hypertension. Brody and associates have recently identified a region of the anteroventral third ventricle (AV3V) that is intimately involved in body fluid homeostasis and arterial pressure regulation. Lesions in this region of the brain prevent the development of experimental renal hypertension, a hypertensive state characterized by high angiotensin levels. It was therefore assumed that a central pressor action of angiotensin was perhaps responsible for initiating and maintaining the elevated blood pressure. Angiotensin-sensitive sites in the region of the third ventricle have been shown to mediate, at least in part, the pressor action of peripherally administered angiotensin. It was further demonstrated, however, that lesions in the anteroventral region of the third ventricle also prevented the development of DOCA-salt hypertension, a low-renin, angiotensin-independent hypertensive model. In the DOCA-salt form of hypertension, any central effects of peripheral angiotensin would be negligible, although the central renin-angiotensin system may remain active.

Bealer et al. have demonstrated that lesioned rats display an impaired ability to excrete a sodium load, and this impairment was due to the virtual absence of natriuretic activity in plasma. An impairment in the release of a natriuretic factor caused by AV3V lesioning could prevent the development of DOCA-salt hypertension if natriuretic hormone is indeed an important pressor agent in this form of hypertension. Haddy et al. have identified a circulating pressor agent postulated to be a natriuretic hormone in low renin hypertension which inhibits Na⁺-K⁺ ATPase activity in vascular tissue. This may secondarily increase contractile activity by altering the Na gradient under in vivo conditions. It has been hypothesized that altered cell Na leads to altered Na - Ca counter-transport and Na - K cotransport. Under the in vitro condition of our experiments, the action of acutely active inhibitory factors such as that studied by Haddy would be washed out. This is supported by our observation of unaltered cellular K concentration in the presence of increased turnover during aldosterone hypertension. This can only be maintained by a compensatory increase in active Na - K transport as observed in DOCA rats. A precise description of the integrative activity of the brain in hormonal control of body fluids, arterial membrane function, pressure regulation and their involvement in hypertensive disease needs further investigation. A recent report suggests that specific mineralocorticoid receptors are present in vascular tissue. The hypertensive effect of chronic aldosterone infusion may be at least in part due to a direct effect of aldosterone on vascular smooth muscle. The sensitizing procedures used to induce mineralocorticoid hypertension (high salt intake and reduced renal mass) may serve to accelerate the hypertensive process by sensitizing the vascular smooth muscle cells to the effects of aldosterone. This could involve either a change in receptor number or affinity in response to a high sodium intake. A thorough description of possible direct effects of aldosterone on vascular smooth muscle and the role of this action in steroid-induced hypertension awaits further study on the binding of aldosterone in vascular tissue, and the physiological effects of this binding.

Acknowledgment

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ALDOSTERONE-INDUCED HYPERTENSION/Garwitz and Jones

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E T Garwitz and A W Jones

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