Vascular Responsiveness in Rats Resistant to Aldosterone-Salt Hypertension

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Wistar-Furth rats have been shown to be resistant to mineralocorticoid-salt hypertension, but the mechanism for this resistance is unknown. In the current experiments, adult male Wistar and Wistar-Furth rats were given a subcutaneous aldosterone infusion (0.15 μg/hr) for 4 weeks, and changes in blood pressure and vascular reactivity were studied. Rats received a 1% NaCl, 0.2% KCl solution to drink. After 4 weeks of aldosterone infusion, systolic blood pressure measured using a tail-cuff technique had increased by 60 mm Hg in Wistar rats but was unchanged in Wistar-Furth rats. Hypokalemia occurred in both strains in response to the aldosterone infusion. Isolated, helically cut strips of common carotid artery and aorta were prepared for isometric force recording. Cumulative concentration–response curves to norepinephrine, serotonin, KCl, calcium, nitroprusside, and acetylcholine were performed in carotid artery strips, and concentration–response curves to ouabain were performed in aortic strips. Increased vascular contractile sensitivity to KCl, ouabain, norepinephrine, and serotonin was observed in vessels from Wistar rats treated with aldosterone and salt. The same treatment in Wistar-Furth rats produced only increased vascular sensitivity to ouabain and serotonin, and these changes were of smaller magnitude than those seen in Wistar rats. Aldosterone-salt treatment produced decreased vascular sensitivity to acetylcholine and nitroprusside in both Wistar and Wistar-Furth rats. These results support the hypothesis that resistance of Wistar-Furth rats to aldosterone-salt hypertension is due to resistance to the effects of aldosterone-salt treatment that normally result in increased vasoconstrictor sensitivity.

Key Words • Wistar rats • Wistar-Furth rats • aorta • carotid arteries • norepinephrine • serotonin • ouabain • acetylcholine • nitroprusside • mineralocorticoid hypertension

Despite long-standing recognition that hypertension can be produced by mineralocorticoid excess, the physiological mechanisms that contribute to the genesis and maintenance of such hypertension are still a matter of debate. One factor that has been suggested to contribute to mineralocorticoid-salt hypertension in experimental animals is changes in the sensitivity of vascular smooth muscle to vasoactive stimuli. An increase in sensitivity to vasoconstrictors such as norepinephrine and serotonin has been demonstrated in vascular preparations from mineralocorticoid-salt–treated rats,1–4 and in some cases these vascular changes have been shown to precede the development of elevated blood pressure.5,6 The changes in vascular reactivity do not seem to be secondary to hypertension per se because protection of vascular beds from high pressure by proximal arterial ligation or antihypertensive therapy does not prevent the appearance of such changes.7,8

It recently has been reported that hypertension does not develop in response to the administration of excess deoxycorticosterone (DOC) and salt in the Wistar-Furth (WF) rat strain.9 The current experiments were designed to test the hypothesis that a lack of development of changes in vascular reactivity is a mechanism involved in the resistance of WF rats to this form of hypertension. Aldosterone was used as the mineralocorticoid in these studies because it is the major mineralocorticoid in rats and to determine whether WF rats are resistant to aldosterone-salt hypertension as well as to DOC-salt hypertension.

Methods

Male Wistar (n=35) and WF (n=32) rats weighing 300–350 g (Harlan Sprague Dawley, Inc., Indianapolis, Ind.) were used. Rats were housed individually in temperature-controlled, 12-hour light/dark-cycled (6 AM–6 PM) quarters with ad libitum access to food and water. All procedures involving the use of animals were approved by the Institutional Animal Care and Use Committee and conformed to institutional, state, and federal guidelines.

After a minimum of 4 days' acclimatization to the animal facility, all rats underwent a right nephrectomy under anesthesia with 45 mg/kg i.p. pentobarbital. Postoperatively, the rats received a subcutaneous injection of 100 mg/kg ampicillin and were given a drinking solution of 1% NaCl, 0.2% KCl in distilled water as their sole source of fluid. After 1 week of postoperative
recovery, a week of control measurements was begun. Fluid intake was measured daily, and body weight and systolic blood pressure (tail-cuff technique with photoelectric detection; IITC Inc., Woodland Hills, Calif.) were determined twice weekly. At the end of the control period, the rats were anesthetized with pentobarbital and an osmotic minipump (Alzet model 2002, Alza Corp., Palo Alto, Calif.) containing a solution of d-aldosterone in polyethylene glycol 400 or the vehicle alone was placed subcutaneously in the intrascapular region. The delivery rate of aldosterone was 0.15 µg/hr. The subcutaneous infusion of aldosterone or vehicle was maintained for 4 weeks. The spent minipumps were replaced with freshly filled minipumps after 2 weeks. During the 4-week infusion period, fluid intake was measured daily and body weight and systolic blood pressure were determined twice weekly. The four experimental groups studied were Wistar rats treated with aldosterone (n = 14), Wistar rats treated with vehicle (n = 14), WF rats treated with aldosterone (n = 16), and WF rats treated with vehicle (n = 16). In a separate group of Wistar rats (n = 7), saline intake was held constant at control levels, and the response to a 4-week subcutaneous aldosterone infusion was determined. This experiment was performed to establish whether increased saline drinking is necessary for the development of hypertension in response to aldosterone.

The rats were anesthetized with 45 mg/kg i.p. pentobarbital at the end of the 4-week treatment period, and a 3-ml blood sample was obtained by abdominal vena cava puncture. Blood samples were centrifuged at 5,000g for 10 minutes. The plasma was removed and stored at −20°C for subsequent determination of the plasma aldosterone concentration by radioimmunoassay (Diagnostic Products Corp., Los Angeles, Calif.) and sodium and potassium concentrations by flame photometry. The hearts were removed, the atria trimmed away, and the weight of the ventricles plus septum recorded.

For vascular reactivity studies, the thoracic aorta and common carotid arteries were removed and placed in cold physiological salt solution (PSS). The arteries were cleaned of excess fat and connective tissue and cut into helical strips under a dissecting microscope. Vascular strips were mounted on metal tissue holders and placed in 50-ml tissue baths filled with warmed (37°C) PSS bubbled with a 95% O2-5% CO2 mixture. Each strip was connected to a model FT.03 force transducer (Grass Instrument Co., Quincy, Mass.) for the measurement of isometric force. Recordings were made on a Grass polygraph. The millimolar composition of the PSS was 130 NaCl, 4.7 KCl, 1.17 MgSO4 • 7 H2O, 1.18 KH2PO4, 14.9 NaHCO3, 5.5 dextrose, 0.03 NaCa2EDTA, and 1.6 CaCl2 • 2 H2O. Vascular strips were allowed to equilibrate for 120 minutes at a passive force of 1.5 g for aorta and 800 mg for carotid artery.

Vascular reactivity experiments were carried out in two separate groups of rats because it was not technically feasible to conduct all protocols in one group. In the first group of rats, concentration-response curves to ouabain were determined in the aorta and concentration-response curves to KCl were determined in the carotid artery. Aortic strips were exposed to 130 mM KCl PSS (made by equimolar substitution of KCl for NaCl in the PSS) in the presence of 2.6 x 10−6 M phentolamine until a steady contractile response was attained. After a 1-hour recovery period, a cumulative concentration-response curve to 10−8 to 10−4 M ouabain was obtained. Aortic strips were exposed to each concentration of ouabain for 15 minutes in the presence of phentolamine. Aortic strips were used for the ouabain experiments for two reasons. First, a marked difference generally exists in ouabain sensitivity in aortas taken from hypertensive and normotensive rats. Second, because of the duration of the ouabain experiment, it was technically not feasible to use ouabain in the strips used for other concentration-response studies.

Cumulative concentration-response curves to KCl in the presence of 2.6 x 10−8 M phentolamine were determined in carotid artery strips. The KCl concentration in the tissue bath was increased by the addition of appropriate volumes of a 3 M KCl stock solution.

In the second group of rats, both carotid arteries were removed and placed in separate tissue baths. In one carotid artery, a concentration-response curve to 2.6 x 10−11 to 2.6 x 10−3 M serotonin was performed. After a 1-hour recovery period, strips were incubated in calcium-free buffer with 1 mM EGTA for 10 minutes after which the strips were stimulated with 2.6 x 10−3 M serotonin. The magnitude of this phasic contraction to serotonin was expressed as a percentage of the tonic contraction to the same concentration of serotonin in 1.6 mM Ca2+ buffer. This phasic contraction was used as an index of the size of the intracellular serotonin-releasable calcium pool. The serotonin was rinsed from the bath with calcium-free buffer, and then the strips were exposed to calcium-free 80 mM KCl buffer (made by equimolar substitution of KCl for NaCl). A concentration-response curve to CaCl2 was then performed. In the second carotid artery, three concentration-response curves (the first to 3 x 10−11 to 3 x 10−8 M norepinephrine, the second to 5.5 x 10−10 to 5.5 x 10−6 M acetylcholine, and the third to 10−11 to 10−7 M nitroprusside) were performed separated by 1-hour recovery periods. The acetylcholine and nitroprusside curves were done in strips precontracted with a concentration of norepinephrine that produced 50% of the maximal response (EC50) (determined from the norepinephrine curve for that strip).

To control for variations in strip size, isometric force was converted to tension. First, the area of each strip was calculated as the weight of the tissue in milligrams divided by the product of the density (1.05 mg/mm2) and length of the strip in millimeters when stretched to its passive force. Tension was then calculated as isometric force (milligrams) divided by area (square millimeters).

**Drugs**

We used the following drugs: norepinephrine bitartrate, serotonin creatinine sulfate, ouabain octahydrate, d-aldosterone, acetylcholine hydrochloride (all from Sigma Chemical Co., St. Louis, Mo.), nitroprusside (Abbott Laboratories, North Chicago, Ill.), and phentolamine mesylate (CIBA Pharmaceutical Co., Summit, N.J.).

**Statistical Analysis**

For calculation of EC50 values for serotonin, norepinephrine, and KCl, contractile responses were expressed as a percentage of the maximal response and a probit analysis was performed. Statistical analysis was performed on the negative logarithm of the EC50 values.
**Results**

Long-term subcutaneous infusion of aldosterone (0.15 μg/hr for 4 weeks) produced a significant increase in systolic blood pressure (Figure 1) in Wistar rats (control, 136±4 mm Hg; week 4, 193±11 mm Hg). The rise in blood pressure developed slowly; a significant increase was first observed 2 weeks after the start of aldosterone infusion. In contrast, there was no significant change in blood pressure in WF rats in response to aldosterone infusion. In a control group, saline was infused instead of aldosterone. The carotid artery strips from WF-aldosterone rats did not exhibit increased sensitivity to KC1 compared with those from control rats (Wistar-vehicle, 17%; WF-vehicle, 15%). Thus, WF rats appear to grow more slowly than Wistar rats.

Although Wistar and WF rats were ordered at the same body weights, by the time the infusion was started, Wistar rats were considerably larger than WF rats. Body weights of the four experimental groups at the start of the infusion were: Wistar-aldosterone, 357±6 g (n=7); Wistar-vehicle, 359±6 g (n=7); WF-aldosterone, 309±4 g (n=8); and WF-vehicle, 294±3 g (n=8). The percentage increase in body weight over the 4-week infusion period was Wistar-aldosterone, 24%; Wistar-vehicle, 23%; WF-aldosterone, 8%; and WF-vehicle, 17%.

Average daily saline intake in the experimental groups (Figure 2) followed a pattern similar to that of the blood pressure response. Average daily intake of a 1% NaCl, 0.2% KCl solution was significantly elevated the first week after the start of aldosterone infusion and remained elevated in Wistar rats (control, 73±5 ml/day; week 4, 108±11 ml/day). Daily saline intake did not change in WF rats in response to aldosterone infusion (control, 46±3 ml/day; week 4, 54±3 ml/day), and intake also remained stable in the two vehicle-treated groups. In the group of Wistar rats that received subcutaneous aldosterone but had their saline intake "clamped" at control levels, hypertension developed over the same time course and to the same degree as in freely drinking Wistar rats. In the rats in which saline intake was restricted, systolic blood pressure rose an average of 61 mm Hg over the 4-week aldosterone infusion period, whereas rats drinking saline ad libitum exhibited an average pressure rise of 60 mm Hg over the same period.

Sensitivity to KCl of carotid artery strips in Wistar-aldosterone rats was significantly greater than that in Wistar-vehicle rats (Figure 3 and Table 1). Carotid artery strips from WF-aldosterone rats did not exhibit increased sensitivity to KCl compared with those from WF-vehicle rats. The maximum tension generated in response to KCl did not differ among groups (Wistar-aldosterone, 3.2±0.5 g; Wistar-vehicle, 3.1±0.5 g; WF-aldosterone, 2.9±0.4 g; and WF-vehicle, 2.8±0.4 g).

**Figure 1.** Plot of systolic blood pressure of Wistar (circles) and Wistar-Furth (triangles) rats in response to subcutaneous infusion of 0.15 μg/hr aldosterone (open symbols) or vehicle (filled symbols). First two data points are control (preinfusion) values; aldosterone or vehicle infusion was begun at vertical dashed line. *p<0.05 different from average of two control values.

**Figure 2.** Plot of average daily saline intake of Wistar (circles) and Wistar-Furth (triangles) rats in response to subcutaneous infusion of 0.15 μg/hr aldosterone (open symbols) or vehicle (filled symbols). Each point is average daily intake over 7-day period. First point is control (preinfusion) value; aldosterone or vehicle infusion was begun at vertical dashed line. *p<0.05 different from control value.
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Figure 3. Concentration–response curves to KCl in carotid arteries from Wistar (circles) and Wistar-Furth (triangles) rats treated with subcutaneous infusion of 0.15 μg/hr aldosterone (open symbols) or vehicle (filled symbols) for 4 weeks. See Table 1 for EC50 values.

Aldosterone, 1,194±227 mg/mm2; Wistar-vehicle, 1,351±141 mg/mm2; WF-aldosterone, 1,371±103 mg/mm2; and WF-vehicle, 1,504±111 mg/mm2.

As shown in Figure 4, the contractile response to 10^-3 M ouabain was significantly greater in aortic strips from Wistar-aldosterone rats than in those from Wistar-vehicle rats. An enhanced response to ouabain was also present in aortic strips from WF-aldosterone rats compared with WF-vehicle rats. Although aldosterone significantly enhanced the ouabain response in both rat strains, the magnitude of the effect depended on the strain (greater in Wistar than in WF rats).

Concentration–response curves for serotonin and norepinephrine in the carotid artery strips are shown in Figure 5 (EC50 values are reported in Table 1). Aldosterone infusion produced a significant increase in carotid artery sensitivity to serotonin in both Wistar and WF rats. In addition, vessels from Wistar rats were more sensitive to serotonin than those from WF rats. Aldosterone infusion did not increase the magnitude of the phasic contraction produced by 2.5x10^-6 M serotonin in calcium-free, 1 mM EGTA buffer in either Wistar or WF rats (Wistar-aldosterone, 29±4%; Wistar-vehicle, 26±4%; WF-aldosterone, 20±2%; and WF-vehicle, 20±2%). Wistar rats did, however, have significantly greater phasic responses to serotonin than WF rats. There was no difference between the groups in maximum tension generated in response to serotonin.

Figure 4. Concentration–response curves to ouabain in aortas from Wistar (circles) and Wistar-Furth (triangles) rats treated with subcutaneous infusion of 0.15 μg/hr aldosterone (open circles) or vehicle (filled symbols) for 4 weeks. % KCl maximum, percentage of contractile response to 130 mM KCl physiological salt solution. Aortas from aldosterone-treated rats were more sensitive to ouabain than those from respective vehicle-treated rats; however, difference was larger for Wistar than for Wistar-Furth rats.

Values are geometric mean of EC50 with 95% confidence interval (CI).
*p<0.05 different from vehicle-treated group of same strain.
Figure 5. Concentration-response curves to norepinephrine (top panel) and serotonin (bottom panel) in carotid arteries from Wistar (circles) and Wistar-Furth (triangles) rats treated with subcutaneous infusion of 0.15 μg/hr aldosterone (open symbols) or vehicle (filled symbols). See Table 1 for EC50 values.

Figure 6. Concentration-response curves to calcium in carotid arteries from Wistar (circles) and Wistar-Furth (triangles) rats treated with subcutaneous infusion of 0.15 μg/hr aldosterone (open symbols) or vehicle (filled symbols). See Table 1 for EC50 values.

Discussion

These experiments were designed to identify physiological mechanisms that underlie the resistance of WF rats to mineralocorticoid-salt hypertension. This rat strain was initially shown to be resistant to adrenal-regeneration hypertension, which is believed to be due to excess production of mineralocorticoids. More recently it has been demonstrated that WF rats are also resistant to hypertension produced by administration of DOC and salt. The resistance to hypertension in the WF strain may be specific to mineralocorticoid hypertension since two-kidney Goldblatt hypertension develops comparably in WF and Sprague-Dawley rats.

Results of the present study confirm and extend the observations of Sciotti and Gallant on DOC-salt hypertension in WF rats. This rat strain also did not become hypertensive in response to long-term subcutaneous infusion of aldosterone (0.15 μg/hr for 4 weeks). In contrast, the Wistar strain exhibited a 60-mm Hg rise in systolic blood pressure over the infusion period. The increment in the plasma aldosterone concentration produced by the infusion was significantly greater in WF than in Wistar rats. This observation rules out the possibility that the lack of a hypertensive response was due to a smaller rise in the plasma aldosterone concent-
tration in WF rats. The increase in the plasma aldosterone concentration produced in these experiments is comparable to what others have found for similar infusion rates. In addition, increases in plasma aldosterone concentrations of comparable magnitude have been reported in rats in response to sodium depletion, adrenocorticotropic hormone infusion, immobilization stress, and two-kidney, one clip renal hypertension. Therefore, the aldosterone infusion rates used in this study produce plasma levels that approximate those seen under “stressed” physiological conditions.

Aldosterone infusion in Wistar rats produced not only an increase in blood pressure but also a significant increase in the daily intake of a 1% NaCl, 0.2% KCl drinking solution. WF rats, in contrast, did not become hypertensive or exhibit increased drinking. Thus, it appears that WF rats are not resistant to all physiological actions of aldosterone. Furthermore, these results suggest that the mechanism responsible for hypokalemia is not sufficient to produce hypertension.

Development of hypokalemia is a characteristic response to mineralocorticoid administration. It is interesting to note that WF rats developed the same degree of aldosterone-induced hypokalemia as Wistar rats even though rats of the former strain did not become hypertensive or exhibit increased drinking. Thus, it appears that WF rats are not resistant to all physiological actions of aldosterone. Furthermore, these results suggest that the mechanism responsible for hypokalemia is not sufficient to produce hypertension. Recently it has been shown that the enhanced vasopressin-stimulated accumulation of cyclic adenosine monophosphate in cortical collecting tubules seen in DOC-salt–treated Wistar rats is also present in DOC-salt–treated WF rats, despite their resistance to hypertension. This study provides additional evidence that some physiological responses to mineralocorticoids are preserved in WF rats.

Alterations in reactivity of the vasculature to both vasoconstrictor and vasodilator stimuli are hallmarks of hypertension. The hypothesis that WF rats do not develop aldosterone-salt hypertension because they do not respond to aldosterone-salt treatment with alterations in vascular reactivity was tested in the current experiments. Isometric contractile responses to four vasoconstrictor stimuli (KCl, ouabain, norepinephrine, and serotonin) were studied. Vascular smooth muscle sensitivity to all four agonists has been demonstrated to be increased in vessels from DOC-salt hypertensive rats compared with vessels from normotensive controls. In addition, norpinephrine sensitivity has been shown to be increased in aortas from aldosterone-salt hypertensive rats compared with aortas from aldosterone-salt hypertensive rats treated with normotensive controls. In normotensive rats, aldosterone infusion was significantly increased, as was the sensitivity of aortas to ouabain. Aldosterone infusion in WF rats differentially affected these contractile responses. Sensitivity to KCl and norpinephrine was unaltered in WF-aldosterone rats compared with WF-vehicle rats. However, vascular sensitivity to ouabain and serotonin was significantly increased in WF-aldosterone rats, albeit the increment in the ouabain response was less than that observed in Wistar-aldosterone rats. It is unlikely that these increases in vascular sensitivity are due to increased calcium sensitivity because calcium sensitivity of potassium-depolarized vessels was actually decreased in

### Table 2. Vasorelaxation in Carotid Arteries From Wistar and Wistar-Furth Rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Acetylcholine [(x10^-7 M)]</th>
<th>Nitroprusside [(x10^-4 M)]</th>
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<td></td>
<td>Mean</td>
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<tr>
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<tr>
<td>Wistar-Furth</td>
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<td>1.2*</td>
</tr>
<tr>
<td>Vehicle</td>
<td>8</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Values are geometric mean of EC50 with 95% confidence interval (CI). Vessels were precontracted with EC50 of norepinephrine.

*p<0.05 different from vehicle-treated group for that strain.
Wistar-aldosterone and WF-aldosterone rats compared with vehicle-infused rats of the same strain. The observation that, under the conditions of these experiments, WF-aldosterone rats exhibited slight increases in vascular sensitivity to ouabain and serotonin suggests that the resistance of WF rats to aldosterone-salt hypertension is relative rather than absolute. That is, the infusion rate of aldosterone that was used in these experiments did not produce hypertension in WF rats over 4 weeks, but this dose may be close to the threshold dose for hypertension in WF rats. It has been shown that WF rats will become hypertensive in response to DOC acetate–salt if the dose of DOC acetate is high enough. The effects of this dose (10 μg/hr) of aldosterone on vascular reactivity in WF rats may indicate that if higher doses were used, WF rats may become hypertensive. Regardless, WF rats were relatively resistant to aldosterone at this infusion rate, whereas Wistar rats exhibited marked hypertension and vascular changes.

The specific cellular mechanisms responsible for the increases in sensitivity to the contractile agonists used in these studies are not known. Increases in KCl sensitivity could be due to membrane depolarization. However, most studies have not demonstrated a difference in in vitro resting membrane potential between hypertensive and normotensive vessels. In fact, the increased potassium efflux that has been observed in aortas from aldosterone-salt hypertensive rats would actually be a hyperpolarizing mechanism. The increased contractile sensitivity to ouabain in isolated vascular smooth muscle in DOC-salt hypertension is generally thought to be secondary to either elaboration of a humoral inhibitor of Na⁺,K⁺-ATPase, which causes upregulation of Na⁺,K⁺-pump sites, or a primary increase in the membrane permeability to sodium, which results in activation of the Na⁺,K⁺-pump. Studies of the mechanism of contractile responses to norepinephrine suggest that enhanced stimulation of the phosphatidylinositol second messenger system in vessels from aldosterone-salt hypertensive rats may be responsible for increased sensitivity to norepinephrine. These same investigators have found no alterations in α-adrenergic receptor number or affinity that could account for the functional differences. Finally, it has been suggested that increased release of calcium from an intracellular store may be a mechanism for increased serotonin sensitivity in DOC-salt hypertension. The results of the present experiments in aldosterone-salt–treated rats and previous experiments in DOC-salt–treated rats do not support this postulate, however, since the phasic response to serotonin in calcium-free buffer was not enhanced in mineralocorticoid-treated rats.

Decreased vascular sensitivity to both endothelium-dependent (acetylcholine) and endothelium-independent (nitroprusside) vasodilators was observed in Wistar-aldosterone rats compared with Wistar-vehicle rats. The same results were obtained in WF rats; aldosterone treatment produced a decreased sensitivity to acetylcholine and nitroprusside. Although many studies have demonstrated impairment of endothelium-dependent relaxation in blood vessels from hypertensive animals, this is not a universal finding and appears to vary with the vascular preparation studied. It also has been suggested that this impaired endothelium-dependent dilation is due to an alteration in endothelial function rather than smooth muscle function because relaxation responses to endothelium-independent dilators such as nitroprusside are unaltered or even enhanced in hypertension. Again, there are discrepancies over this point in the literature because impaired relaxation responses to sodium nitroprusside have been observed in vessels from hypertensive rats. Results of the current experiments suggest that decreased endothelium-dependent vasodilation may be associated with a generalized decrease in the sensitivity of cyclic guanosine monophosphate–dependent dilatory mechanisms and that aldosterone-salt treatment produces decreases in acetylcholine and nitroprusside sensitivity even in the absence of hypertension (as was seen in WF rats). Interestingly, we found that nitroprusside produced a 180% relaxation of norepinephrine-induced contraction in Wistar-aldosterone rats (i.e., nitroprusside produced relaxation to below baseline tension). This result, coupled with the observation that calcium-free solution produced relaxation in vessels from Wistar-aldosterone rats, suggests that carotid arteries from these rats had significant resting tone that was not observed in any other group.

The mechanism (or mechanisms) by which administration of aldosterone or other mineralocorticoids produce alterations in vascular reactivity is unclear. Mineralocorticoids have been shown to have direct effects on vascular smooth muscle in vitro. These actions include a decrease in free intracellular sodium secondary to stimulation of Na⁺,K⁺-ATPase and potentiation of contractile responses to catecholamines, probably by inhibition of extraneuronal uptake. In the whole animal, both hyper-
tension and changes in vascular reactivity in response to mineralocorticoid administration depend on elevated NaCl intake because neither are observed in rats with a normal sodium intake.21 Central administration of 6-hydroxydopamine to selectively deplete brain catecholamines prevents DOCA-salt hypertension and alterations in vascular reactivity,58 suggesting that integrity of brain structures is necessary for DOC to produce changes in vascular reactivity. In view of the uncertainties about whether mineralocorticoids act directly on vascular smooth muscle or secondary to some other mechanism in the whole animal to alter vascular reactivity, no conclusions can yet be made as to the mechanism by which WF rats are resistant to the effects of aldosterone and salt on in vitro vascular reactivity.

In summary, aldosterone-salt treatment produced hypertension and increased arterial blood pressure, intrinsic calcium-dependent vascular tone, and increased vascular contractile sensitivity to KCl, ouabain, norepinephrine, and serotonin in Wistar rats. The same treatment in WF rats produced only increased vascular sensitivity to ouabain and serotonin, and the magnitude of these changes was not as great as that seen in Wistar rats. Aldosterone-salt treatment produced decreased vascular sensitivity to acetylethanolamine and nitroprusside in both Wistar and WF rats. Similar increases in the plasma aldosterone concentration and decreases in the plasma potassium concentration resulted from aldosterone infusion in both strains. These results support the hypothesis that resistance of WF rats to aldosterone-salt hypertension is due to resistance to the effects of aldosterone-salt treatment that normally result in increased vasoconstrictor sensitivity.

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