Calcium Sensitivity of Isometric Force in Intact and Chemically Skinned Aortas during the Development of Aldosterone-Salt Hypertension in the Rat

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SUMMARY. We investigated the role of altered vascular calcium handling in the development of aldosterone-salt hypertension in the rat. The calcium sensitivity of isometric force in response to 50 mM KCl was compared in aortic rings from control and aldosterone-hypertensive rats. Over the entire range of calcium concentrations studied, responses in aortas from the hypertensives were significantly depressed compared to controls [ED50: aldosterone-hypertensive rats (n = 6), 0.739 ± 0.137; controls (n = 7), 0.141 ± 0.021 mM; P < 0.001]. However, calcium sensitivity in response to 1 μM norepinephrine was similar in aortas from both hypertensives and controls [ED50: aldosterone-hypertensive rats (n = 7), 0.196 ± 0.022; controls (n = 7), 0.180 ± 0.024 mM]. The calcium sensitivity of Triton X-100 skinned aortic rings from aldosterone-hypertensive rats was likewise not significantly different from sensitivity in controls [ED50: aldosterone-hypertensive rats (n = 9), 3.61 × 10^-7 ± 0.57; controls (n = 8), 3.89 × 10^-7 ± 0.64 M]. Therefore, the observed decrease in calcium sensitivity in response to membrane depolarization in aortas from aldosterone-hypertensive rats probably is not due to a change in calcium sensitivity of the contractile system itself. The time course for development of changes in calcium handling in vessels from the aldosterone-hypertensive rats was found to be quite different from the time course for changes in monovalent ion metabolism. Whereas increases in monovalent ion permeability reportedly appear as early as one week after the start of aldosterone-salt treatment, significant alterations in calcium handling were not apparent until after four weeks of treatment. After one week of aldosterone-salt treatment, calcium sensitivity in response to 50 mM KCl was similar in aortas from the aldosterone-treated rats compared to controls. After two weeks, the ED50 for calcium sensitivity in response to 50 mM KCl was slightly increased in the aldosterone-treated group, compared to controls. Therefore, the trend appears to be a progressive decrease in calcium sensitivity in aortic smooth muscle during the development of aldosterone-salt hypertension in the rat. This reduction in calcium sensitivity appears to be primarily a membrane phenomenon; it is unlikely that it reflects alterations in the contractile system itself. (Circ Res 56:427-435, 1985)
have reported that aortas from SHR are leakier to extracellular calcium (Webb and Bhalia, 1976; Noon et al., 1978). A recent study by Mulvany and Nyborg (1980) using small mesenteric resistance vessels from SHR indicated that small vessel sensitivity to calcium in hypertension differs substantially from large vessel responsiveness. Mesenteric resistance vessels from SHR were found to be more sensitive to calcium than controls, when stimulated with NE, but not when stimulated with high potassium. These findings suggest an abnormality in receptor-operated calcium channel function but normal potential-sensitive activation processes in SHR resistance vessels. It is not clear to what extent abnormalities in calcium handling might contribute to the elevated pressure in this form of experimental hypertension.

An alteration in calcium sensitivity in vessels from hypertensives could be the result of a change at a number of possible sites in the excitation-contraction coupling scheme. A change in membrane permeability to calcium might be considered a logical candidate, since vascular permeability to monovalent ions—sodium, potassium, and chloride—has been shown to be increased significantly in large arteries from hypertensive animals (Jones, 1983). Changes in cytoplasmic calcium removal mechanisms—calcium uptake into the sarcoplasmic reticulum and active calcium transport via a sarcolemmal Ca++ ATPase—may also lead to an alteration in calcium responsiveness. There is some evidence from work using isolated microsomal membrane fractions that calcium removal mechanisms in arteries from hypertensives might be inadequate (Moore et al., 1975; Twietmeyer et al., 1978; Kwan et al., 1979). Alternatively, a change in the calcium sensitivity of the regulatory mechanisms for the contractile system may underlie the alteration in calcium sensitivity in vessels from hypertensives. This possibility can be directly tested by measuring calcium sensitivity in a chemically skinned vascular smooth muscle preparation that is devoid of functional plasma membrane and intracellular calcium pools. In such a system, the calcium sensitivity of the contractile system itself can be directly evaluated.

This approach was recently utilized by Nghiem and Rapp (1983) to evaluate calcium sensitivity in tail artery from SHR. They reported that calcium sensitivity in skinned SHR tail artery was similar to that in a skinned preparation from Dahl salt-resistant rats. These results would suggest that alterations in calcium sensitivity in the SHR are not the result of an altered calcium responsiveness of the contractile system itself. However, this conclusion is not straightforward, because interpretation of data from the SHR model is known to be quite sensitive to the type of control animal used (Seidel, 1979).

The present study was undertaken to determine whether the calcium handling properties of aortas from aldosterone-salt hypertensives rats (AHR) are altered during the development of this form of experimental hypertension. This model of mineralocorticoid-dependent hypertension is of particular interest, in that hypertension is produced with physiological doses of aldosterone (Garwitz and Jones, 1982a). Aorta from AHR have been shown to have substantially altered membrane permeabilities to sodium, potassium, and chloride (Garwitz and Jones, 1982a, 1982b), as well as a significantly elevated basal oxygen consumption rate (McMahon and Paul, 1984). In this study, the calcium sensitivity of both intact and chemically skinned aortas from AHR was determined, so that the role of altered calcium metabolism in the development of this form of experimental hypertension could be assessed.

**Methods**

**Animals and Tissues**

The aldosterone-hypertensive rat model has been described in detail elsewhere (Garwitz and Jones, 1982a, 1982b). Briefly, the left kidney was removed from anesthetized male Sprague-Dawley rats (150-200 g). An osmotic mini-pump (Alza) containing d-aldosterone (Sigma) dissolved in polyethylene glycol, or vehicle only for the control group, was implanted subcutaneously in the animals. Aldosterone was infused into the rats at 0.25 μg/hr. Control rats were given a 1% (wt/vol) NaCl solution to drink, whereas the aldosterone-treated animals also received a supplement of KCl (0.3% wt/vol) in the NaCl solution to aid in the maintenance of body weight. Systolic blood pressure was measured using a tail cuff technique (Friedman and Freed, 1949).

On the morning of the experiment, the rats were killed and the thoracic aortas were rapidly removed. The aortas were cleaned of adventitia and adherent fat and then cut transversely into rings. One 6-mm ring was mounted isometrically in a glass chamber (volume = 1.8 ml) for measurement of force. A second ring (approximately 1 mm) was mounted in a system used for measurement of isometric force in chemically skinned vascular smooth muscle. At the end of each experiment, the segments were cut open longitudinally, and muscle dimensions (segment length and circumference) were then measured by microscopy, using an ocular scale. The tissues were then gently blotted and weighed.

**Intact Vascular Preparation**

The physiological solution (PSS) had the following composition (mm): Na+, 146.2; K+, 5.0; Mg++, 1.2; Ca++, 2.5; Cl-, 143.9; HCO3-, 13.5; H2PO4-, 1.2; and glucose, 11.4. Ca++-free PSS was similar to PSS with the exclusion of CaCl2 and the addition of 0.2 mM ethyleneglycol-bis (β-amino-ethyl ether)-N,N′ tetraacetic acid (EGTA). Solutions were gassed with a mixture of 95% O2/5% CO2 at 37°C. The measured pH of these solutions was typically between 7.3 and 7.4. Solutions of norepinephrine (L-norepinephrine bitartrate; Sigma) were made by dissolving NE in PSS. Ethylenediamine tetraacetic acid (EDTA, 0.026 mM) was added to these solutions to delay oxidation of the drug. Depolarization-induced contractions were elicited by the addition of KCl (45 μM) from a concentration (2 mM) to increment the bath concentration by 50 mM.

Isometric measurements of force were made on intact vessel segments with a Kistler-Morse transducer (compliance = 0.1 μm/mN). Vessel cross-sectional area was calculated according to A = 2 × wet weight/1.06 × C, where
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1.06 g/cm³ is used as an estimate of tissue density and C is vessel circumference.

Skinned Vascular Preparation

A 1-mm aortic ring was mounted horizontally between a movable and fixed post, the movable end attached to a force transducer (AME 801, Aksjeselskapet Mikro-elektronik). The ring was bathed initially in a morpholinopropane sulfonic acid (MOPS)-buffered PSS solution in a 0.4-ml Lucite bath. The ionic species in MOPS-PSS were similar to that of the bicarbonate-buffered PSS, with the exclusion of NaHCO₃ and the addition of 2 mM MOPS. Experiments were conducted with solutions equilibrated with room air at 37°C.

The aortic rings were chemically skinned by a modification of the procedure described by Rüegg and Paul (1982). The following solutions were used for skinned fiber experiments at 25°C: presoak solution (PS)—20 mM imidazole, 5 mM EGTA, 50 mM KCl, and 150 mM sucrose (pH 7.4); skinning solution—PS + 5% Triton X-100, 0.5 mM dithioerythritol (DTE), 1 mM phenylmethyl sulfonyl fluoride (PMSF); relaxing solution (RS), containing (mM) — K⁺, 21; Na⁺, 36; Mg⁺⁺(total), 10; EGTA, 4; ATP, 7.5; imidazole, 20; Cl⁻, 35; azide 1; an ATP-regenerating system consisting of 10 mM phosphocreatine, and 10 U/ml of creatine phosphokinase, pH 6.7; contracting solution (CS)—EGTA was partly replaced with Ca²⁺-EGTA to increase the free Ca²⁺. The concentration of free Ca²⁺ was calculated by means of the calculator program provided by Fabiato and Fabiato (1979). The absolute stability constants used in the program are those compiled by Fabiato (1981).

Statistical Methods

Values are presented as the mean ± SEM. Significance was determined by Student’s t-test; a probability of less than 0.05 was regarded as statistically significant.

Experimental Protocol

Tissues were equilibrated initially for a period of 2 hours in PSS at 37°C. During equilibration, the tissues were stretched in a step-wise fashion until a stable force of approximately 7–10 mN/mm segment length was achieved. We have previously determined that a passive tension of this magnitude occurs at a length that is optimal for active force development in aortas from both the control and hypertensive rats (McMahon and Paul, 1984). Calcium sensitivity in the intact vessels was determined in response to both potassium depolarization (50 mM KCl) and norepinephrine stimulation (1 μM NE). The protocol used to measure calcium sensitivity in response to potassium depolarization (50 mM KCl) and norepinephrine stimulation (1 μM NE). The protocol used to measure calcium sensitivity in response to potassium depolarization (50 mM KCl) and norepinephrine stimulation (1 μM NE). The protocol used to measure calcium sensitivity in response to potassium depolarization (50 mM KCl) and norepinephrine stimulation (1 μM NE). The protocol used to measure calcium sensitivity in response to potassium depolarization (50 mM KCl) and norepinephrine stimulation (1 μM NE). The protocol used to measure calcium sensitivity in response to potassium depolarization (50 mM KCl) and norepinephrine stimulation (1 μM NE). The protocol used to measure calcium sensitivity in response to potassium depolarization (50 mM KCl) and norepinephrine stimulation (1 μM NE). The protocol used to measure calcium sensitivity in response to potassium depolarization (50 mM KCl) and norepinephrine stimulation (1 μM NE). The protocol used to measure calcium sensitivity in response to potassium depolarization (50 mM KCl) and norepinephrine stimulation (1 μM NE). The protocol used to measure calcium sensitivity in response to potassium depolarization (50 mM KCl) and norepinephrine stimulation (1 μM NE). The protocol used to measure calcium sensitivity in response to potassium depolarization (50 mM KCl) and norepinephrine stimulation (1 μM NE). The protocol used to measure calcium sensitivity in response to potassium depolarization (50 mM KCl) and norepinephrine stimulation (1 μM NE). The protocol used to measure calcium sensitivity in response to potassium depolarization (50 mM KCl) and norepinephrine stimulation (1 μM NE). The protocol used to measure calcium sensitivity in response to potassium depolarization (50 mM KCl) and norepinephrine stimulation (1 μM NE).
hypertensive rat. Following a test contracture with 50 mM KCl, the vessels were exposed to calcium-free solution containing 0.2 mM EGTA, then repeatedly stimulated with 50 mM KCl and 1 mM NE. This procedure effectively depletes the tissue of intracellular calcium stores, as indicated by the small response to the third application of NE + KCl in Figures 1 and 2. The vessel was then depolarized with 50 mM KCl in calcium-free solution (no EGTA), and the isometric tension response to increasing concentrations of calcium was recorded. The isometric tension responses to the cumulative addition of calcium were considerably slower in the aorta from the AHR (Fig. 2) compared to the intact aortic rings was illustrated in Figure 3, using aortic rings from an aldosterone-hypertensive rat. Before skinning, the isometric tension response to the addition of 50 mM KCl was recorded in the intact tissue at 37°C. After the bath temperature was lowered to 25°C, the ring was exposed to a 5% Triton solution for 10 minutes, then rinsed briefly in "relaxing solution" (see Methods). The isometric tension response to increasing concentrations of free Ca++ was then recorded to obtain the Ca++ dose-response relationship.

Results

After 4 weeks of infusion, systolic blood pressure in the aldosterone-salt treated group was elevated substantially compared to controls (Table 1). The calcium sensitivity of aortas from these animals was investigated using the protocol depicted in Figures 1 and 2. After depletion of internal calcium stores, the isometric tension response to increasing extracellular calcium concentrations was recorded in depolarized vessels. The results from a series of these experiments are summarized in Figure 5. Isometric tension responses in both the controls and hypertensives have been normalized to the force attained at 2.5 mM Ca++ in each group. Maximal active stress in response to 2.5 mM Ca++ was similar in controls and hypertensives [C: (n = 7), 30.00 ± 2.62; AHR: (n = 5), 27.90 ± 2.41 mN/mm2]. Active stress values for each experimental series are henceforth included in the figure legends. Over the entire range of calcium concentrations studied, responses in aortas from the aldosterone hypertensives were significantly depressed when compared to controls. In addition, the shape of the two curves was quite
different. Responses in the controls reached a plateau level at low concentrations of Ca**, while steady state tension responses in the hypertensives increased in an almost linear fashion over the entire range of extracellular calcium levels tested. The ED50 for calcium in aortas from the hypertensives rats was increased 5-fold compared to controls (Table 1). These results indicate that the sensitivity to extracellular calcium induced by membrane depolarization was reduced in vessels from hypertensives compared to controls.

To determine whether calcium sensitivity was similarly altered in vessels from the hypertensives under conditions in which receptor-operated channels are thought to mediate contraction, we examined the dependence of isometric force on extracellular calcium in response to a maximal dose of norepinephrine (1 μM) as described above (see Experimental Protocol). As shown in Figure 6, calcium sensitivity in response to 1 μM NE was similar in aortas from the control and hypertensive rats. The ED50 for calcium in controls [(n = 7) 0.180 ± 0.024 μM] was not significantly different from the value calculated for the hypertensive group [(n = 7) 0.196 ± 0.022 μM].

The reduced calcium sensitivity in response to depolarization in vessels from hypertensives may reflect an alteration in the excitation-contraction coupling scheme at numerous possible sites. One possibility is that the change in calcium sensitivity is due to altered calcium responsiveness of the contractile system itself. This can be evaluated by measuring calcium responsiveness in a chemically skinned vascular preparation in which the ability of the plasmalemma and other intracellular organelles to buffer cytoplasmic calcium levels has been removed. In such a system, isometric tension responses to increases in extracellular calcium will reflect the calcium sensitivity of the contractile system itself. The protocol for detergent skinning used in this study was detailed previously (see Experimental Protocol, Figs. 3 and 4). As shown in Figure 7, skinned aortic rings contracted substantially in response to an increase in extracellular calcium concentration. Tension responses in skinned aortas from AHR tended to be slightly lower than responses in controls, although maximal force at pCa = 4.9 was not significantly different in the two groups (Fig. 7).
1.00

FIGURE 6. Calcium dose-response relationship in responses to 1 μM
norepinephrine in aortic rings from control (○, n = 7) and aldosterone-
hypertensive rats (□, n = 7). Isometric tension responses have been
normalized to the force obtained at 2.5 mM Ca** in each vessel [C (n = 7), 24.44 ± 2.54; AHR: (n = 7), 20.96 ± 2.65 mN/mm²]. Each
symbol represents the mean ± SEM except where the symbol size
exceeds the SEM.

These maximal responses in the skinned aortas represented 88 ± 12% (AHR, n = 7) and 127 ± 29% (C, n = 6) of responses to KCl obtained in intact
aortic rings before skinnig. The ED50 for calcium in skinned aortas from the AHR was not significantly
different from the value obtained in controls (Table 1). These results indicate that the calcium sensitivity
of the contractile system is similar in aortas from control and hypertensive rats. Therefore, the ob-
served decrease in calcium sensitivity in response to depolarization in intact vessels from hypertensives
is not due to a change in the sensitivity of the contractile system, itself, to calcium.

Vascular permeability to monovalent ions has been reported to be increased significantly in aortas
from aldosterone-hypertensive rats as early as 1 week after the start of aldosterone-salt treatment
(Garwitz and Jones, 1982b). If changes in membrane permeability to calcium follow a similar time course,
then calcium permeability may likewise be increased early in the course of the hypertension development.
Therefore, the decrease in calcium sensitivity in response to KCl depolarization observed after 4
weeks of aldosterone treatment in the present study may be compensatory to early increases in calcium
influx. To investigate this possibility, we measured calcium sensitivity in response to 50 mM KCl in
aortas from rats receiving the aldosterone-salt treatment for 1 week and compared it with aortas from
age-matched controls receiving 1% NaCl for a similar period of time. After 1 week, systolic blood
pressure was marginally elevated in rats receiving aldosterone, compared with controls (Table 1). Al-
though this elevation in pressure was statistically significant, a systolic pressure of 133 mm Hg is
similar to previously published values for controls (Jones et al., 1977; Garwitz and Jones, 1982a), and
is considered to fall within the normal range for the rat. As shown in Figure 8, calcium sensitivity in
response to 50 mM KCl in aortas from the aldosterone-treated rats was similar to controls over the
entire range of extracellular calcium concentrations studied. The ED50 in the aldosterone-treated group
was not significantly different from controls (Table 1).

A second group of animals received the aldosterone-salt treatment for a period of 2 weeks. Systolic
blood pressure in these animals was significantly elevated compared with controls receiving 1% NaCl
for 2 weeks (Table 1). However, calcium sensitivity in response to 50 mM KCl was not significantly
different in aortas from the two groups (Fig. 9). Although the ED50 for calcium was slightly increased
in the hypertensives compared with controls (Table 1), this difference was not statistically significant.
These results do not support the hypothesis that the decrease in calcium permeability under KCl-depo-
larizing conditions observed after 4 weeks of aldostereone infusion is compensatory to early increases
in vascular permeability to calcium. Rather, the trend appears to be a progressive decrease in this
calcium permeability during the course of hypertension development.

Aortic segments from the 1- and 2-week aldosterone-treated and control rats were also subjected to
detergent treatment, and calcium sensitivity in these skinned aortic preparations was determined by the
protocol previously described. The results from
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• Control, 1 week
O Aldosterone, 1 week

FIGURE 8. Calcium dose-response relationship in response to 50 mM KCl in aortic rings from controls (•, n = 6) and rats infused with aldosterone for 1 week (O, n = 6). Isometric tension responses have been normalized to the force obtained at 15 mM Ca²⁺ in each vessel [C: (n = 6), 25.79 ± 3.97; A: (n = 6), 27.49 ± 3.59 mN/mm²]. Each symbol represents the mean ± SEM, except where the symbol size exceeds the SEM.

these experiments are summarized on Table 1, along with systolic blood pressure data and calcium ED₅₀ levels in intact aortas from the 1-, 2-, and 4-week groups. As with the 4-week animals, after 1 and 2 weeks of aldosterone-salt treatment, the ED₅₀ for calcium in the skinned aortas was similar to the value obtained in aortas from age-matched normotensive controls. In addition, these values were similar to values obtained in aortas from rats receiving aldosterone for 4 weeks. Therefore, at no time during the course of hypertension development was there an alteration in the calcium sensitivity of the contractile system itself.

Discussion

The calcium sensitivity of isometric force in response to membrane depolarization with high potassium was significantly reduced in aortas from AHR compared to controls. This reduction in sensitivity was not due to an altered calcium sensitivity of the contractile system itself, since calcium sensitivity was similar in chemically skinned aortas from control and hypertensive rats. Furthermore, in response to a maximal dose of norepinephrine, the dependence of isometric force on extracellular calcium in intact aortas from AHR was not significantly different from the calcium sensitivity in aortas from control rats.

It has been proposed that, in smooth muscle, calcium influx stimulated by KCl depolarization occurs through potential-operated calcium channels, whereas NE receptor occupation stimulates calcium influx through a distinct receptor-operated pathway (Bolton, 1979; Van Breemen et al., 1982). In addition, NE receptor occupation stimulates release of calcium from intracellular stores (Van Breemen et al., 1980). Meisheri and coworkers (1981) demonstrated that the NE-stimulated influx of Ca²⁺ was additive to that induced by KCl-depolarization, and was not as sensitive to blockade by Ca²⁺ antagonists. These data suggest that calcium influx through potential-operated and receptor-operated calcium channels occurs through two distinct pathways. Therefore, the reduction in calcium sensitivity in response to KCl-depolarization in aortas from the AHR suggests an alteration exclusively in potential-operated calcium handling in these vessels. Since calcium sensitivity in response to NE in AHR aortas was similar to that of controls, it is unlikely that intracellular calcium storage and release mechanisms are involved. The reduced level of calcium sensitivity in response to membrane depolarization is thus likely to result from either a reduction in the potential-mediated calcium influx and/or an enhanced rate of calcium efflux in the AHR aorta.

Two calcium extrusion mechanisms have been proposed to operate in vascular smooth muscle, active calcium transport via Ca²⁺-ATPase and Na⁺-Ca²⁺ exchange (Van Breemen et al., 1979). It is currently a matter of debate which mechanism is more crucial to the maintenance of cellular calcium homeostasis, although the bulk of experimental evidence appears to favor the former mechanism (Van Breemen et al., 1982). An enhanced rate of calcium pumping as a mechanism responsible for the reduced calcium sensitivity in AHR would be consistent with previously documented metabolic changes in aortas from AHR (McMahon and Paul, 1984). We have demonstrated that the rate of both basal and stimulated ATP utilization in aortas from AHR are enhanced significantly compared to controls, and that it is unlikely that these increases are due to enhanced Na⁺-K⁺ transport or inefficient energy utilization by the contractile machinery. An elevated
rate of calcium extrusion via a Ca\textsuperscript{++}-ATPase is a possible factor underlying this enhanced energy utilization in AHR, although further study is required to test this hypothesis adequately. On the other hand, it is not possible to rule out decreased calcium influx in response to membrane depolarization as a potential factor underlying the reduced calcium sensitivity in aortas from the hypertensives. Calcium influx studies would be required to assess this possibility adequately.

This study indicates that the time course and directionality of changes in calcium metabolism during the development of aldosterone-salt hypertension in the rat differ substantially compared to alterations in monovalent ion metabolism. Passive membrane permeability to potassium and chloride in rat aorta is increased as early as 1 week after the initiation of aldosterone-salt treatment, and permeability increases steadily as the hypertension progresses (Garwitz and Jones, 1982b). In contrast, calcium sensitivity in response to membrane depolarization, while unchanged after 1 week of aldosterone-salt treatment, decreased progressively during the development of hypertension. Thus, changes in calcium handling appear to lag somewhat behind changes in monovalent ion metabolism. This result suggests that a resetting of membrane excitation mechanisms through changes in passive permeability to Na\textsuperscript{+}, K\textsuperscript{+}, and Cl\textsuperscript{-} might play a more important causal role in the development of aldosterone-salt hypertension than changes in calcium-handling properties.

In contrast to most previous reports on calcium sensitivity in arteries from mineralocorticoid hypertensive rats, our study demonstrates that the development of this form of hypertension is not always accompanied by an enhancement of arterial calcium sensitivity. Whereas calcium responsiveness to NE remained unchanged during the course of hypertension development in SHR aorta, potential-mediated calcium sensitivity actually decreased compared to controls. This reduction in calcium sensitivity in aortas from AHR may not be unique to mineralocorticoid-dependent hypertension, since Pedersen and coworkers (1978) report a similar reduction in SHR aortas, although others have reported an enhanced calcium sensitivity (Holloway and Bohr, 1973; Noon et al., 1978; Mulvany and Nyborg, 1980). These discrepant results obtained in studies using vessels from SHR may partially reflect the diverse ages of the SHR used, as well as the control animal utilized. In mineralocorticoid-dependent models in the rat, the divergent results may be due to differences in the artery chosen for study, since caudal artery (Hinke, 1966) has been compared to femoral (Holloway and Bohr, 1973), carotid (Bohr, 1974), and mesenteric arteries (Kwan et al., 1979). Although a consensus on the importance of alterations in calcium handling in hypertension is not possible at this time, it is clear that responses in a particular type of hypertension may be quite different compared to responses in other forms of the disease. Moreover, within a given model of hypertension, calcium-handling responses in different arteries may also be unique. Our results indicate that the altered level of calcium sensitivity in response to membrane depolarization in aortas from AHR is primarily a membrane phenomenon and probably does not reflect alterations in the regulatory mechanisms of the contractile system itself.

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INDEX TERMS: Vascular smooth muscle • Hypertension • Aldosterone • Salt (NaCl) • Chemical skinning • Calcium sensitivity
Calcium sensitivity of isometric force in intact and chemically skinned aortas during the development of aldosterone-salt hypertension in the rat.

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Circ Res. 1985;56:427-435
doi: 10.1161/01.RES.56.3.427

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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