Altered Ion Transport in Vascular Smooth Muscle from Spontaneously Hypertensive Rats

INFLUENCES OF ALDOSTERONE, NOREPINEPHRINE, AND ANGIOTENSIN

By Allan W. Jones

ABSTRACT

The interaction of vascular electrolytes and early spontaneous hypertension was studied in the rat aorta. Chemical composition (H$_2$O, Na, K, Ca, Mg, Cl, collagen, and elastin), extracellular space, and cell water content were little changed. Only uronic acid and hexosamine contents were significantly elevated in the spontaneously hypertensive rat. Approximately 37% of the aortic weight was cellular. Functional changes in ion transport were observed in smooth muscle from hypertensive rats; the muscle exhibited decreased ability to accumulate K and extrude Na and increased turnover of $^{42}$K ($0.0165 \pm 0.0009$ vs. $0.0086 \pm 0.0002$ min$^{-1}$) and $^{36}$Cl ($0.162 \pm 0.011$ vs. $0.118 \pm 0.003$ min$^{-1}$). Spontaneously hypertensive rats maintained increased $^{42}$K exchange after adrenalectomy and reserpine. The bioregulants, aldosterone, norepinephrine, and angiotensin had important actions on ion exchange. After adrenalectomy, aldosterone therapy reduced $^{42}$K exchange toward intact levels. Norepinephrine increased the rate of $^{42}$K exchange with the dose-response relation having a lower median effective dose (ED$_{50}$) for spontaneously hypertensive rats ($10^{-9}$ g/ml) than it did for normal Wistar rats ($2 \times 10^{-9}$ g/ml). Angiotensin also increased $^{42}$K exchange with similar dose-response relations for both groups. I concluded that functional alterations observed in spontaneously hypertensive rats probably resulted from primary changes in ion transport by vascular smooth muscle rather than from secondary effects of altered regulatory systems. The decreased selectivity to K over Na and the increased turnover of ions could lead to increased reactivity to norepinephrine through effects on membrane potentials.

KEY WORDS collagen elastin mucopolysaccharide

aortic water and electrolytes $^{42}$K and $^{36}$Cl exchange corticosterone

adrenalectomy dose response vascular reactivity blood pressure

Increased water and electrolyte contents of the arterial wall have been associated with experimental hypertension of renal and steroid origin (1, 2). Such changes are thought to be important in the development of increased vascular stiffness and peripheral resistance. A strain of rats which spontaneously develops hypertension has recently become available as a model for essential hypertension (3), but little change in the water, sodium, or potassium content of aortas from these rats has been observed during the early hypertensive phase (13 weeks old) (4). This observation raises the question of the role of vascular electrolyte metabolism in the pathogenesis of spontaneous hypertension and perhaps of other types of the disease.

The objective of the present study was to reappraise the interaction of vascular electrolytes and spontaneous hypertension. Since ion transport by smooth muscle is especially important for regulating total wall contents (5, 6), the experimental approaches investigated functional properties as well as total wall composition. The influences of bioregulators were also studied to clarify points regarding hyperreactivity and to separate primary
Analyses of Tissues from 10-15-Week-Old Rats

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Type of rat</th>
<th>N</th>
<th>(%) wet wt</th>
<th>H2O (kg/kg dry solid)</th>
<th>Na</th>
<th>K</th>
<th>Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aorta</td>
<td>Sprague Dawley</td>
<td>8</td>
<td>69.2 ± 0.8</td>
<td>2.26 ± 0.08</td>
<td>252 ± 6</td>
<td>125 ± 5</td>
<td>142 ± 4</td>
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<td>Aorta</td>
<td>SHR</td>
<td>13</td>
<td>65.3 ± 0.7</td>
<td>1.80 ± 0.06</td>
<td>295 ± 9</td>
<td>125 ± 5</td>
<td>141 ± 4</td>
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<td>Aorta</td>
<td>Wistar</td>
<td>12</td>
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<td>1.80 ± 0.06</td>
<td>292 ± 5</td>
<td>123 ± 5</td>
<td>139 ± 4</td>
</tr>
<tr>
<td>Diaphragm</td>
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<td>12</td>
<td>76.5 ± 0.2</td>
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<td>142 ± 4</td>
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<td>3.5</td>
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<tr>
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<td>76.4 ± 0.3</td>
<td>3.24 ± 0.05</td>
<td>139 ± 6</td>
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<td>3.6</td>
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<tr>
<td>Tendon</td>
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<td>12</td>
<td>57.8 ± 0.8</td>
<td>1.38 ± 0.05</td>
<td>172 ± 4</td>
<td>43 ± 5</td>
<td>4.3</td>
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<tr>
<td>Tendon</td>
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<td>13</td>
<td>58.1 ± 0.6</td>
<td>1.40 ± 0.03</td>
<td>174 ± 4</td>
<td>42 ± 3</td>
<td>5.8</td>
</tr>
</tbody>
</table>

Values are means ± se. SHR = spontaneously hypertensive Kyoto Wistar rats.

from secondary alterations in smooth muscle transport.

**Methods**

**Animal and Tissue Preparations.**—Male Kyoto Wistar (3) spontaneously hypertensive rats used for this study were obtained from Carworth Red Lion. Control male rats were normal Wistar rats (as primary controls) from Carworth Red Lion, Sprague Dawley rats from Carworth Red Lion, normal Wistar rats from Huntingdon Farms, and rats of the Charles River CD strain; normal Kyoto Wistar rats were not available. All the studies were carried out on rats 10-15 weeks old. Control rats weighed 300 g, and hypertensive rats weighed 250 g. The rats were stunned and decapitated and tissues were removed for fresh analyses. For in vitro experiments, the thoracic aorta was placed in potassium free aerated dissection solution at 37°C, trimmed of loose connective tissue, cut along its length, and mounted on a stainless steel holder. The strips were transferred to the experimental solution after 2 hours. Aortas routinely accumulated potassium to within 10% of the level found in fresh tissue, after 3 hours in the control physiological solution.

Before decapitation, blood pressures were measured directly with catheters inserted into the tail artery under ether anesthesia 24 hours earlier. Mean pressures were measured in unanesthetized rats with a manometer (Statham P23Gb) and a rectilinear recorder (Sanborn).

Adrenalectomies were performed by the supplier 8-10 days before experimentation. The rats were maintained on saline drinking water. Post-mortem examinations were routinely performed, and no adrenal glands were found. Rats receiving replacement therapy were given (in oil) either aldosterone acetate (300 μg/kg, im) 20 hours before decapitation or corticosterone (15 mg/kg, im) for 7 days with the last injection 20 hours before experimentation. Controls received sesame oil only. Rats treated with reserpine received 0.2 mg/kg, ip, in distilled water 20 hours before experimentation and 0.4 mg/kg 6-8 hours later (7, 8).

**Solutions.**—Solutions were prepared from double-distilled water and analytic grade reagents. The control physiological salt solution employed had the following millimolar composition: Na⁺ 146.2, K⁺ 10.0, Mg²⁺ 1.2, Ca²⁺ 2.5, Cl⁻ 148.9, HCO₃⁻ 13.5, H₂PO₄⁻ 1.2, and glucose 5.7. All solutions were bubbled with 97% O₂ - 3% CO₂ at 37°C (measured pH 7.4). The control solution was modified for the dissection by omitting K and lowering Ca to 0.025 mM. This reversibly depleted the tissue of endogenous K. Solutions containing norepinephrine or angiotensin amide were made by serial dilution with medium containing 0.025 mM ethylenediaminetetraacetate (EDTA). The solution for determining extracellular space contained ⁶⁰CoEDTA (0.2-0.5 μc/ml) plus CoEDTA (2 mM) (6, 9). The loading solution for the washout experiments contained either ⁴⁰K (10-30 μc/ml) or ⁴⁰Cl (1-2 μc/ml).

**Isotope Techniques.**—Strips of aorta were equilibrated with isotope 3-5 hours after removal from the dissection solution. Following a 1-2-second rinse, the tissues were passed through a series of tubes containing nonradioactive solution. A description of the precautions taken and an evaluation of the washout procedure appear elsewhere (6, 9). The activity in the tubes and tissues was counted in a gamma well counter (⁴⁰K) or by liquid scintillation techniques (⁴⁰Cl). Exchange curves were calculated by sequentially adding the tissue and the tube counts in reverse order and normalizing in terms of percent of initial activity (6).

**Chemical Analyses.**—Methods were essentially the same as those previously employed (6). Water content was determined by weight difference after oven drying (20 hours at 93°C). Electrolytes extracted from ashed tissues were analyzed by atomic absorption spectroscopy (Perkin Elmer, model 303). Collagen and elastin contents were determined by the method of Neuman and Logan (11) as modified by Fisher and Llaurado (12). Mucopolysaccharides were released by acid hydrolysis (13). Hexosamine was measured by the

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ION TRANSPORT AND HYPERTENSION

Mg ± 0.3 =t 0.4 * 0.2 =fc 1.0 =*= 1.0 =t 0.8 ± 0.7
Cl ± 12 ± 11 ± 8 =*= 3 ± 3 =<= S ± 6

Collagen Elastin (%dry wt)

24.0 ± 1.0
21.4 *
20.6 =t 0.6

37.7
39.0 =* 3.8
36.9

Collagen plus elastin
57.5 ± 0.9

Collagen/elastin
0.64 ± 0.02
0.55 ± 0.01
0.56 ± 0.02

Hexuronic acid (mM Ag d »
28.9 =t 1.0
22.3 =t 0.5
26.0 =t 1.1

Croni acid (mM Ag d »
24.0 =t 1.0
22.3 =t 0.5
26.0 =t 1.1

method of Grant et al. (13). Hexuronic acid was assayed by the carbazol technique of Bitter and Muir (14).

Data Processing.—The computations for the washout experiments were done by digital computer. Rate constants were computed from the time (t) required for the slow component to progress to 1/e of the initial percent (determined by extrapolation to t = 0. The rate constant k = 1/t. This technique allows accurate representation for a component following a single exponential rate constant or for one exhibiting a statistically distributed rate constant (5, 15). Significance was tested by Student's t-test.

Results

Tissue Contents and Water Distribution

The mean blood pressure of the spontaneously hypertensive rats used in this study was 158 ± 6 mm Hg (N = 6) vs. 106 ± 5 mm Hg for the normal Wistar rats (N = 6). The chemical composition (Table 1) of fresh tissues from the spontaneously hypertensive rats was essentially the same as that of tissues from Wistar rats except for an elevation in aortic uronic acid (P < 0.001) and hexosamine contents (P < 0.025). Aortas removed from Sprague Dawley rats exhibited intermediate mucopolysaccharide levels and elevated collagen-elastin ratios, calcium, and H2O (P<0.01). Therefore, only minor compositional changes were apparent in the spontaneously hypertensive rats, a finding which confirms that of Nagaoka et al. (4). Also, spontaneous hypertension was not associated with major alterations in the distribution of aortic water (Table 2): approximately 37% of the aortic weight was cellular (mostly smooth muscle) based on cell water estimates (Table 2) and dry solid analyses (Table 1).

Potassium Accumulation

The possibility of a functional alteration in Na-K transport by smooth muscle was then explored. It has been observed in a variety of smooth muscles that the accumulation of K with increasing extracellular K concentration follows a sigmoid relation with a plateau being achieved over the physiological K concentration range (16–18). As K is accumulated by these smooth muscles, Na levels decrease with the ratio of extracellular Na to extracellular K required for half maximum uptake being indicative of the overall selectivity of the Na-K transport processes (16–18). The K accumulation curve for aortas of spontaneously hypertensive rats was shifted to the right in comparison with that for aortas of Wistar rats (Fig. 1). At an extracellular Na concentration of 150 mM, 1.25 mM extracellular K was required for 50% response in spontaneously hypertensive rats, whereas Wistar rats achieved similar levels at 0.94 mM, representing a shift in selectivity for Na-K transport from 160 (150/0.94) in Wistar rats to 120 (150/1.25) in spontaneously hypertensive rats. The shift was estimated to be significant at the 5% level, in that direct comparisons between Wistar and spontaneously hypertensive rats in the region of 20–80% uptake (at extracellular K concentrations of 1.0 mM and 1.5 mM) indicated a consistent decrease in uptake for spontaneously hypertensive rats (P < 0.005 and <0.05, respectively). This decreased ability to accumulate K and extrude Na was supported by comparison of estimated smooth muscle Na and K contents (Table 3). The Na contents fell as the K contents increased with increasing extracellular K concentrations, but

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POTASSIUM TURNOVER

The reduced ability of aortas of spontaneously hypertensive rats to accumulate K could result from several factors. One possibility, increased turnover or "leakiness" to K, was tested. Increased washout of $^{42}$K was observed in the aortas of spontaneously hypertensive rats (Fig. 2) under conditions in which both groups started at similar levels of K (extracellular K concentration of 10 mM). The slow component analyzed has been shown to be associated with smooth muscle transport (16, 17). The rate of exchange for a series of spontaneously hypertensive rats was 80-90% greater ($P < 0.001$) than that for the control groups (Table 4). The various strains of normotensive rats in contrast exhibited similar rates of turnover.

Washouts of ${}^{36}$Cl were examined to determine whether increased K turnover was part of a more general alteration. Spontaneously hypertensive rats exhibited an increased turnover (Fig. 3) with a rate constant of $0.182 \pm 0.011$ min$^{-1}$ ($n = 6$) vs. $0.118 \pm 0.003$ min$^{-1}$ ($n = 6$) for Wistar rats ($P < 0.005$). Both groups contained similar levels of slowly exchanging ${}^{36}$Cl. This component was primarily regulated by smooth muscle transport as indicated by increased loss during application of norepinephrine (Fig. 3).

VASCULAR CONTROL SYSTEMS

Since endocrine, neural, and renal systems are known to play an important role in circulatory control and in the pathogenesis of hypertension, the possibility was explored that altered K turnover in aortas of spontaneously hypertensive rats might reflect a control abnormality rather than an alteration in smooth muscle per se.

TABLE 3

<table>
<thead>
<tr>
<th>Extracellular K concentration (mM)</th>
<th>Na</th>
<th>K</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SD</td>
<td>W</td>
</tr>
<tr>
<td>0</td>
<td>113 ± 14 (10)</td>
<td>119 ± 8 (12)</td>
</tr>
<tr>
<td>0.5</td>
<td>95 ± 13 (9)</td>
<td>118 ± 12 (9)</td>
</tr>
<tr>
<td>1.0</td>
<td>62 ± 6 (18)</td>
<td>65 ± 6 (15)</td>
</tr>
<tr>
<td>1.5</td>
<td>59 ± 7 (10)</td>
<td>57 ± 8 (12)</td>
</tr>
<tr>
<td>2.0</td>
<td>57 ± 3 (9)</td>
<td>62 ± 8 (9)</td>
</tr>
<tr>
<td>5.0</td>
<td>60 ± 3 (8)</td>
<td>51 ± 3 (14)</td>
</tr>
<tr>
<td>10.0</td>
<td>52 ± 4 (16)</td>
<td>38 ± 6 (10)</td>
</tr>
</tbody>
</table>

Values are means ± SE; number of rats tested is indicated in parentheses.

$*P < 0.01$.  

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TABLE 4

<table>
<thead>
<tr>
<th></th>
<th>SHR*</th>
<th>SHR†</th>
<th>Wistar</th>
<th>Wistar†</th>
<th>Sprague-Dawley*</th>
<th>Sprague-Dawley†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.0106 ± 0.0009 (3)</td>
<td>0.0102 ± 0.0006 (5)</td>
<td>0.0103 ± 0.0007 (3)</td>
<td>0.0102 ± 0.0006 (5)</td>
<td>0.0104 ± 0.0008 (7)</td>
<td>0.0102 ± 0.0006 (5)</td>
</tr>
<tr>
<td>Adrenalectomy</td>
<td>0.0099 ± 0.0006 (5)</td>
<td>0.0096 ± 0.0008 (3)</td>
<td>0.0096 ± 0.0008 (3)</td>
<td>0.0096 ± 0.0008 (3)</td>
<td>0.0098 ± 0.0008 (7)</td>
<td>0.0096 ± 0.0008 (3)</td>
</tr>
<tr>
<td>Adrenalectomy + aldosterone</td>
<td>0.0102 ± 0.0006 (5)</td>
<td>0.0102 ± 0.0006 (5)</td>
<td>0.0102 ± 0.0006 (5)</td>
<td>0.0102 ± 0.0006 (5)</td>
<td>0.0102 ± 0.0006 (5)</td>
<td>0.0102 ± 0.0006 (5)</td>
</tr>
</tbody>
</table>

Values are means ± s.e.; number of rats tested in parentheses; SHR = spontaneously hypertensive rats.

Adrenal Steroids.—The removal of steroids by adrenalectomy resulted in increased \(^{42}\)K turnover...

FIGURE 2

Representative steady-state washouts of \(^{42}\)K for Wistar (W) (•) and spontaneously hypertensive (SHR) (o) rats. Individual points are joined by straight lines. Counts are expressed as percent of initial counts (log scale) vs. time. Note that the percent remaining after 1 minute was similar for both groups of rats in this and subsequent figures.

FIGURE 3

Washout of \(^{22}\)Cl from Wistar (•) and spontaneously hypertensive (o) rats plotted as in Figure 2. Individual points are averages for six rats ± s.e. and are joined by straight lines. The passage of tissues through tubes containing norepinephrine (N-epi) (10\(^{-7}\) M) is indicated by the horizontal bar.
(Fig. 4, Table 4) with little change in K levels at an extracellular K concentration of 10 mM. Spontaneously hypertensive rats continued to exhibit faster turnover than did Wistar rats ($P < 0.001$). Replacement therapy with aldosterone acetate reduced rates of $^{42}$K exchange toward those found in unoperated rats ($P < 0.01$); however, spontaneously hypertensive rats still retained higher rates than did Wistar rats (Fig. 4, Table 4). Replacement therapy with corticosterone studied in a second series of Wistar rats had a smaller effect (Table 4).

**Norepinephrine.**—Reserpinized spontaneously hypertensive rats exhibited increased $^{42}$K turnover in comparison with treated Wistar rats ($P < 0.001$) (Figs. 5 and 6); however, reserpinization was related to reduced rates for both groups ($P < 0.01$). The application of norepinephrine increased the rate of $^{42}$K washout in a dose-dependent manner. The fraction exchanged per minute in spontaneously hypertensive rats (Fig. 5) exhibited a small but sustained increase at $10^{-10}$ g/ml, but only a transient response was observed in Wistar rats. The effects of high doses were investigated in a second series of reserpinized rats (Fig. 6). Norepinephrine ($10^{-7}$ g/ml) yielded changes that were similar to those shown in Figure 5. Higher doses yielded no additional increase in the response, with the spontaneously hypertensive rats exceeding controls at all doses. The principal effect of higher concentrations was to reduce the rate of recovery during the wash periods. The dose-response relations were derived by normalizing the maximum response for each dose in terms of the maximum response at $10^{-7}$ g/ml (Fig. 5) and are plotted in Figure 7. The relation for spontaneously hypertensive rats was shifted to the left with a median effective dose ($ED_{50}$) of $10^{-9}$ g/ml vs. $2 \times 10^{-8}$ g/ml for Wistar rats.

**Angiotensin.**—Reserpinized rats were employed to evaluate direct effects on smooth muscle. Angiotensin was applied for only 5 minutes (vs. 15 minutes for norepinephrine, Fig. 5) with wash periods of 55 minutes (vs. 25 minutes, Fig. 5) to...
reduce the effects of tachyphylaxis (19). Angiotensin increased the rate of $^{42}$K washout in a dose-dependent manner (Fig. 8). Both groups exhibited similar increases in rate for the two lower doses. In contrast to norepinephrine, angiotensin resulted in a smaller response in spontaneously hypertensive rats than it did in Wistar rats over higher dose levels. The dose-response relations (Fig. 9), although suggestive of increased reactivity in spontaneously hypertensive rats in response to low doses, were not statistically different.

**Discussion**

Vascular smooth muscle can participate in circulatory control by acting as an integrator of inputs from neural, renal, endocrine, and local control systems or as an effector producing changes in vascular stiffness by graded contractions. Changes in ionic permeability are important factors coupling these two functions through influences on the membrane potential and the availability of calcium for contraction (20-22). For instance, norepinephrine and angiotensin depolarize vascular smooth muscle (23) and increase ion turnover (present study, 21, 22). Furthermore, the dose-response relations for $^{42}$K exchange are in the same range as those for contraction in rat aorta (19, 24), indicating that changes in permeability may act as a controlling mechanism for effector function. The finding that replacement therapy with aldosterone altered K turnover is especially important in
developing concepts for adrenal-cardiovascular interactions.

This study provided evidence for the association of increased K and Cl permeability of vascular smooth muscle with early spontaneous hypertension in the rat. This increased permeability was observed when alterations in gross ionic composition of the aorta were not apparent. The increased aortic mucopolysaccharide levels, however, may have reflected early effects of high blood pressure on the arterial wall (25). The persistence of increased ionic turnover in spontaneously hypertensive rats (1) under in vitro conditions (for at least 10 hours), (2) after adrenalectomy, and (3) following reserpine supports the hypothesis that involvement of smooth muscle transport is a primary rather than a secondary alteration dependent on abnormal outputs from sympathetic and adrenal control systems. There is precedent for genetically linked transport alterations as evidenced by the strain of sheep having low-potassium red blood cells (26). Because of the polygenic dependence of blood pressure in spontaneously hypertensive rats (27, 28) additional changes may be anticipated. Investigations of renin-angiotensin systems (29–31), catecholamine metabolism (32–34), and steroid secretion (35), however, have not established primary alterations. This fact further supports the conclusion that altered vascular K and Cl exchanges are primary rather than secondary manifestations.

The decreased ability of spontaneously hypertensive rats to accumulate K and extrude Na at low extracellular K concentrations indicates the involvement of Na-K-coupled transport as well. Although the steady-state Na-K levels represent the net effect of several transport processes, e.g., diffusion and adsorption onto selective molecules, it is indicative of a decreased selectivity to K over Na in spontaneously hypertensive rats. The plateau for K accumulation (over the range of extracellular K concentrations employed) probably did not represent maximum uptake. Recent studies have confirmed that like skeletal muscle vascular smooth muscle can take up additional K when the extracellular Na is completely replaced by extracellular K (10).

Increased turnover of ions and decreased selectivity of vascular smooth muscle to K over Na in spontaneously hypertensive rats may have contributed to the resetting of the dose-response relation for norepinephrine. It is tempting to speculate that such alterations in ionic permeability and selectivity could result in depolarization of the resting potential given the normal concentration gradients for smooth muscle (10, 36). A partial depolarization would shift the operating point toward levels associated with increased flux changes and resultant contractile activity in response to norepinephrine and would represent resetting of the integrator function of vascular smooth muscle. Measurements of resting potentials in spontaneously hypertensive rats and in Wistar rats would be helpful in establishing this point. This approach to the question of hyperreactivity differs from, but does not exclude, the approach of Folkow and coworkers (37, 38) which emphasizes changes in vascular geometry. Presumably, with continued increased smooth muscle activity and high blood pressure, structural changes would occur leading to decreased radius-wall thickness ratio, which in turn would contribute to increased peripheral resistance.

A number of precautions should be noted before extending the present findings to general theories about the pathogenesis of hypertension. One is the appropriateness of the controls. Great care was taken to use different strains, to match controls with the spontaneously hypertensive rats for each experimental day and to repeat crucial experiments (42K washout) over an extended period (15 months). The availability of normal Kyoto Wistar rats would help firm up the observations, although comparison of two separate colonies of Wistar rats indicated only small genetic drift for normal 42K turnover. A second note of caution lies in the extrapolation of findings on large blood vessels to behavior primarily controlled by small arteries or arterioles. There is, however, evidence for qualitatively similar changes in ionic composition of both large and small vessels from rats with renal hypertension (39, 40). Also, continued hypertension in spontaneously hypertensive rats is associated with increased aortic weight (4) and structural changes at the arteriolar level (41). Although general involvement of vascular smooth muscle in spontaneously hypertensive rats would be expected, direct confirmation of the current findings in small arteries will be necessary. Finally, hypertension takes several forms with different suspected etiologies and experimental models, e.g., renal and steroid, spontaneously hypertensive rats are but one model. The role of altered smooth muscle transport in other forms of hypertension remains to be explored. There is evidence for gross changes in ionic composition in renal and steroid models (1); however, the question of primary and secondary factors remains unsettled. Studies which combine...
cellular and systems approaches to the control of vascular behavior should help clarify these issues.

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References


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