Potassium Preserves Endothelial Function and Enhances Aortic Compliance in Dahl Rats

Krishnankutty Sudhir, Theodore W. Kurtz, Paul G. Yock, Andrew J. Connolly, R. Curtis Morris, Jr

It has recently been proposed that in rat models of genetic hypertension, supplemental dietary potassium preserves release of endothelium-derived relaxing factor independently of its capacity to either attenuate hypertension or increase plasma potassium. To test this hypothesis in Dahl salt-sensitive rats given sodium chloride (4%) for 3 weeks, we supplemented dietary potassium (2.1%) with either KCl (n=16) or KHCO3 (n=16). Compared with unsupplemented rats (n=16), rats supplemented with either potassium salt had a lower mean arterial pressure and a greater release of endothelium-derived relaxing factor, as assessed from acetylcholine-induced relaxation of precontracted aortic rings. However, the maximum relaxation response to acetylcholine correlated inversely with blood pressure (r=-.82, P<.001), not only in the KCl (r=-.68, P<.002) and KHCO3 (r=-.77, P<.001) groups but also in unsupplemented rats (r=-.86, P<.001). With potassium supplementation, plasma potassium concentrations measured between 4 and 6 PM did not increase, but those measured between 4 and 6 AM did increase (P<.05). In isolated ring segments, aortic compliance was greater in both the KCl and KHCO3 groups than in unsupplemented rats (0.015 and 0.017 vs 0.009 mm2/mm Hg) (P<.01). This greater compliance could not be related to differences in blood pressure, plasma potassium, or collagen or elastin content of the aortic wall. In salt-loaded Dahl salt-sensitive rats in which supplemental dietary potassium attenuates hypertension, (1) the extent to which release of endothelium-derived relaxing factor is preserved is directly related to the extent to which potassium restricts the salt-induced rise in blood pressure, (2) nocturnal but not diurnal plasma potassium is increased, and (3) aortic compliance is enhanced. (Hypertension. 1993;22:315-322.)

KEY WORDS • endothelium-derived relaxing factor • hypertension, sodium-dependent • potassium • compliance

By modulating the contractile state of vascular smooth muscle subjacent to the site of its release, endothelium-derived relaxing factor (EDRF) is a major physiological determinant of vascular tone,1 regional blood flow,2 and systemic arterial blood pressure.3 The extent to which EDRF release can be induced is a measure of endothelial function and can be indirectly assessed in vitro from the extent to which acetylcholine induces vasodilation in aortic rings precontracted with norepinephrine.4-5 In recently published studies using this technique for this assessment,4-5 supplemental dietary potassium is reported to preserve the release of arterial EDRF in the salt-loaded, hypertensive Dahl salt-sensitive (DS) rat4 and in the salt-loaded, hypertensive stroke-prone spontaneously hypertensive rat (SHRSP).5 Because either pharmacological or surgical attenuation of hypertension can preserve or restore arterial EDRF release,6-8 supplemental dietary K+ might preserve EDRF release by its antihypertensive effect alone.9-11 But in the studies of both the DS rat and SHRSP,4,5 it is contended that supplementation of dietary K+ preserved EDRF release without attenuating hypertension and hence that this capacity of potassium is independent of its antihypertensive effect.

Yet in the study of the SHRSP under consideration,5 attenuation of hypertension throughout the initial 4-week period of K+ supplementation14 might account for the preserved release of EDRF observed 4 weeks after,5 even though at that time, hypertension was found to be not attenuated. And in the study of the DS rat, supplemental dietary K+ that preserved EDRF release did in fact also attenuate hypertension, except when the mean blood pressure of the K+-supplemented rats was compared with that of a small subgroup of unsupplemented rats selected post hoc for the lowest values of blood pressure.4 Furthermore, in this subset, mean EDRF release was greater than that measured in the unsupplemented group as a whole. Accordingly, supplemental dietary potassium might preserve EDRF release only to the extent that it restricts the rise in blood pressure induced by salt loading. We report a positive test of this hypothesis in the current study of a large group of salt-loaded DS rats in which supplemental dietary K+ predictably attenuated hypertension.11

In the aforementioned studies of SHRSP and DS rats,4,5 it is also contended that supplementation of dietary K+ preserved EDRF release without increasing the plasma concentration of potassium. Indeed, in both

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models of hypertension, it might appear that dietary supplementation of potassium attenuates hypertension without inducing an increase in the plasma concentration of K⁺. Because rats feed mainly at night, supplementing dietary K⁺ might increase the nocturnal but not diurnal plasma concentration of potassium. We report a positive test of this hypothesis.

In many studies, dietary K⁺ supplementation has been shown to reduce systolic blood pressure more than diastolic blood pressure. Systolic blood pressure can be caused by reduced arterial compliance. Antihypertensive agents such as nitrovasodilators and converting enzyme inhibitors that mainly lower systolic blood pressure are said to do so by exerting a relaxing effect on arterial smooth muscle that increases arterial compliance. In the current study, we determined whether supplemental K⁺ preserved arterial compliance and whether the demonstrated preservation could be related to attenuation of hypertension. Finally, because the chloride ion may exert vasoconstrictive effects of its own and the chloride moiety of potassium chloride might constrain the antihypertensive effect of potassium, we examined the effects of supplementation with both potassium chloride (KCl) and potassium bicarbonate (KHCO₃) on blood pressure and vascular function.

Methods

Animals and Diet

Four- to 5-week-old inbred male DS rats (SS/Jr strain) were obtained from Harlan Sprague Dawley Inc, Indianapolis, Ind, and individually housed in metabolic cages.

All rats were fed a high sodium chloride (NaCl) diet prepared by supplementing Purina Rat Chow with 40 g/kg NaCl (the basal NaCl content of the chow before addition of supplemental NaCl was 0.58%; the basal potassium content was 1.1%). Experimental animals were fed the high NaCl diet supplemented with 2.1% potassium provided in the form of either KCl or KHCO₃. Control animals were fed the high NaCl diet without supplemental potassium. A pair-feeding protocol was followed to ensure that the daily food intake for each group was nearly identical. Distilled water was provided ad libitum. All studies were conducted in accordance with the guidelines of the Committee on Animal Research, University of California, San Francisco.

Blood Pressure Measurements

After 3 weeks of rats on either the control or experimental diet, the mean arterial pressure (MAP) of each rat was measured in the unanesthetized, unrestrained state through indwelling femoral artery catheters. Each rat was briefly anesthetized with methoxyflurane, and a catheter (PE 50) was implanted in the femoral artery, the distal end being tunneled subcutaneously to an exit at the nape of the neck. The catheter was filled with a heparinized solution of 5% dextrose and plugged with a stainless-steel obturator. After surgery, each rat was returned to its cage to recover from anesthesia; blood pressures were measured 3 days after the anesthetic agent was stopped at a time (1 to 4 PM) when the animals were fully alert and roaming freely within their cages.

For measurement of blood pressure, the femoral catheter was connected via an extension catheter (PE 50) to a low-volume pressure transducer (model P50, Gould Inc, Cleveland, Ohio). The measurement of blood pressure was begun 30 to 60 minutes after the catheter was connected to the transducer. The output of the transducer was routed to a Gould preamplifier and the MAP signal passed to an analog-to-digital convertor (DASH-8, Metrabyte Co, Taunton, Mass) installed in an IBM AT microcomputer. Data acquisition software was used to sample the blood pressure signal every 15 seconds over a period of 2 hours. The average of these 480 measurements obtained over 2 hours was then calculated to yield the MAP of each animal.

Measurements of Plasma and Urine Concentrations of Potassium and Other Electrolytes

Heparinized blood samples were obtained after measurement of MAP. The first sample (approximately 1 mL) was collected between 4 and 6 PM. The animals were then returned to their cages and given ad libitum access to their respective diets. A second blood sample was then collected between 4 and 6 AM on the following day. With each sample, the blood was immediately centrifuged and the plasma obtained for subsequent measurement of potassium concentration (flame photometry). Blood pH and bicarbonate were also measured with a blood gas analyzer (Radiometer America Inc, Westlake, Ohio). Urinary sodium and potassium were measured from 24-hour collections (flame photometry), and cumulative excretion over the entire 3-week treatment period was calculated.

Measurements of In Vitro Aortic Endothelium-Derived Relaxing Factor Release and Compliance

Perfusion apparatus and imaging device. Twenty-four to 48 hours after the second blood sample was collected, the rats were killed by decapitation. The descending thoracic aorta was harvested after carefully cannulating its side branches. A 25-mm segment was suspended in a perfusion apparatus containing physiological salt solution with the following composition (mM): Na⁺, 144; K⁺, 4.7; Ca²⁺, 2.5; Mg²⁺, 1.2; H₂PO₄⁻, 1.2; Cl⁻, 128.7; HCO₃⁻, 25; SO₄²⁻, 1.2; SCN⁻, 1.2; glucose, 11; and EDTA, 0.027, aerated with a gas mixture of 95% O₂ and 5% CO₂ and maintained at 37°C. The vessel was continuously perfused with physiological salt solution from a 1 L capacity reservoir using a pulsatile peristaltic pump (Cole-Parmer Instrument Co, Chicago, 111). Perfusion pressure was monitored continuously from a side arm with a pressure transducer (Statham) connected to a polygraph (Chart, MacLab/4, Analog Digital Instruments, Palo Alto, Calif). Vascular dimensions were measured in vitro using two-dimensional ultrasonic imaging in a manner similar to that previously described. In brief, an ultrasound transducer (20 MHz) was suspended beside the vessel, and cross-sectional images were generated with a CVIS Insight system (Cardiovascular Imaging Systems, Sunnyvale, Calif). Images were continuously recorded on videotape for subsequent off-line analysis. Selected portions of the videotape were digitized (8 bits, Rasterops 324, Santa Clara, Calif) and stored on a computer disk. An observer who was blinded to which diet the rat received performed mea-
measurements of cross-sectional area using specialized software developed in our laboratory.

Response to acetylcholine. For pharmacological experiments, a perfusion pressure of 70 mm Hg was selected. Although this was lower than in vivo pressure, previous in vitro studies in vessels of different sizes have shown that the maximum active tension in response to pharmacological agonists was generated at a transmural pressure of approximately 60 to 70 mm Hg.28-30 All vessels were thus studied at identical transmural pressures to minimize the confounding effect of variable perfusion pressures on local EDRF release. Aortic segments were precontracted by perfusion with phenylephrine (1 μM) for 10 minutes. Measuring cross-sectional areas at 1 log M increments in acetylcholine concentrations (0.1 nM to 0.1 mM), we generated cumulative concentration-response curves. The vessel was perfused for 5 minutes at each concentration. In addition, to study endothelium-independent vasodilation, we examined the relaxation response produced by a near-maximal concentration of sodium nitroprusside (0.1 μM, 10 minutes) in vessels precontracted with phenylephrine (1 μM, 10 minutes).

Measurement of compliance. Aortic segments were perfused at pressures increasing from 20 to 200 mm Hg in steps of 20 mm Hg. At each pressure, cross-sectional images were recorded for subsequent off-line analysis of cross-sectional areas. Because the volume of a cylinder equals cross-sectional area times length, for a vessel of fixed length, cross-sectional area is directly proportional to volume. In each vessel, the relation of pressure to cross-sectional area was examined to measure vascular compliance.

Histological examination. At the end of each experiment, aortas were fixed in 10% neutral buffered formalin, embedded in paraffin, and sectioned at 5 μm thickness. A section from each vessel was then stained with Verhoeff’s elastin and Masson’s trichrome stain, which stains elastin fibers black and collagen blue. Color micrographs and stage micrometer images were videotaped with a Zeiss microscope equipped with a color CCD camera. As with ultrasound images, selected portions of the videotape were digitized (Rasterops 324) and stored on computer disk. Media thickness was measured with specialized software developed in our laboratory. With the use of computer-assisted colorimetry, the number of black pixels in a high power field, representative of elastin content, was measured and normalized to the total number of pixels in the field to obtain an “elastin index.” Similarly, a “collagen index” was quantitated from the number of blue pixels in sections stained with the elastin trichrome stain.

Calculations and Statistical Analysis

For concentration-response curves to acetylcholine, the range of response to phenylephrine was used as a reference (100%), and results were expressed as the percentage of relaxation in response to cumulative dose increments of drug. EC50 values and Emax (maximum relaxation) for each vessel were calculated. In the case of the compliance curves, the slope of the linear part of the pressure–cross-sectional area relation (0 to 180 mm Hg) was calculated for each vessel. Comparisons among the three groups were performed using analysis of variance and a Student-Newman-Keuls test. Correlations between blood pressure and plasma concentration of potassium to estimates of EDRF release (ie, maximum response to acetylcholine, Emax) and compliance (slope of the pressure–cross-sectional area relation) were examined using linear regression by the least-squares method. Differences between the regression lines for the relation between blood pressure and EDRF release across the three groups were assessed using the overall test for coincidental regressions.31 Results are expressed as mean±SEM, and the null hypothesis was rejected at a value of P<.05.

Results

Blood Pressure and Body Weight

MAP was significantly lowered and to the same extent in both groups treated with potassium salts (control, 150±2.6; KCl, 130±1.6, P<.001; KHCO3, 134±3.3 mm Hg, P<.005) (Fig 1). Body weight at 3 weeks was lower in the KCl group but not the KHCO3 group compared with control, although total food intake was not different (Table).

Plasma and Urine Potassium and Other Electrolytes

Diurnal K+ concentrations were not significantly different from control in the KCl group but were 7% lower in the KHCO3 group (P<.05, Table). Nocturnal plasma potassium was significantly higher in the potassium-treated rats (P<.05) and higher in the KHCO3 than in the KCl group (P<.05) (Table). Blood bicarbonate was lower in the KCl-treated group compared with control, but blood pH was not different. Total urinary sodium excretion was 8% lower in the KCl-treated group compared with control, but blood pH was not different. Total urinary potassium excretion was 2.4-fold higher in the KCl group and 2.6-fold higher in the KHCO3 group compared with control (see the Table).

Effect of Potassium on Endothelium-Dependent Relaxations

There was no significant difference among the three groups in the vasoconstrictor response to phenylephrine (1 μM) as determined by a decrease in cross-sectional area. Maximum relaxation to acetylcholine (Emax) was
Table 1. Physiological Variables in Unsupplemented Control Rats and Rats Supplemented With Either KCI or KHCO3

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>KCI</th>
<th>KHCO3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>230.8±5.4</td>
<td>210.3±5.1*</td>
<td>218.9±5.3</td>
</tr>
<tr>
<td>Total food intake (g/3 wk)</td>
<td>375.9±5.1</td>
<td>365.7±7.2</td>
<td>372.3±8.1</td>
</tr>
<tr>
<td>Plasma K+ at 4 PM (mmol/L)</td>
<td>3.56±0.04</td>
<td>3.54±0.05</td>
<td>3.31±0.04*</td>
</tr>
<tr>
<td>Plasma K+ at 4 AM (mmol/L)</td>
<td>3.69±0.04</td>
<td>4.21±0.08†</td>
<td>4.61±0.08†</td>
</tr>
<tr>
<td>Blood pH at 4 PM</td>
<td>7.42±0.01</td>
<td>7.41±0.01</td>
<td>7.42±0.01</td>
</tr>
<tr>
<td>Blood pH at 4 AM</td>
<td>7.47±0.01</td>
<td>7.45±0.01</td>
<td>7.47±0.01</td>
</tr>
<tr>
<td>Blood HCO3 at 4 PM (mmol/L)</td>
<td>22.81±0.54</td>
<td>22.35±0.59</td>
<td>22.56±0.46</td>
</tr>
<tr>
<td>Blood HCO3 at 4 AM (mmol/L)</td>
<td>26.17±0.49</td>
<td>24.21±0.73†</td>
<td>26.58±0.46</td>
</tr>
<tr>
<td>Total urinary Na+ excretion (mmol/3 wk)</td>
<td>238.9±4.4</td>
<td>220.2±5.7*</td>
<td>241.9±7.0</td>
</tr>
<tr>
<td>Total urinary K+ excretion (mmol/3 wk)</td>
<td>69.7±1.3</td>
<td>165.5±4.5†</td>
<td>183.3±5.1†</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Measurements were made after 3 weeks on experimental diet unless otherwise indicated. *P<.05, †P<.01, ‡P<.001 vs control.

significantly greater in the potassium-treated groups (F=6.87, P=.002 by analysis of variance) (Fig 2). When data from all 48 animals were pooled, there was a strong inverse correlation between the \( E_{\text{max}} \) in response to acetylcholine and MAP (\( r=-.82, P<.001 \)) (Fig 3). This inverse relation of \( E_{\text{max}} \) to MAP was also seen in each of the individual groups (control, \( y=208.04-0.93x, r=-.96, P<.001 \); KCI, \( y=211.6-0.91x, r=-.68, P<.002 \); KHCO3, \( y=206.7-0.87x, r=-.77, P<.001 \), where \( x \) is MAP and \( y \) is the maximum response to acetylcholine), with no significant difference in the regression lines among groups (overall test for coincidental regressions, \( F=0.38, \text{NS} \)). There was, however, no relation of \( E_{\text{max}} \) in response to acetylcholine to plasma potassium levels, either diurnal or nocturnal. There was no significant difference in EC50 values in response to acetylcholine among the three groups (control, 8.36±0.05; KCI, 8.35±0.06; KHCO3, 8.22±0.05 –log M). The relaxation response to the endothelium-independent vasodilator sodium nitroprusside (0.1 \( \mu \)M) was greater than 90% in all three groups (control, 92±4%; KCI, 97±3%; KHCO3, 93±5%).

Effect of Potassium on Vascular Compliance

In the compliance experiments, the slope of the pressure–cross-sectional area relation was significantly increased by potassium supplementation but to a similar degree in the KCI and KHCO3 groups (control, 0.009±0.0005; KCI, 0.015±0.0006, \( P<.01 \); KHCO3, 0.017±0.0007 mm2/mmHg, \( P<.01 \)) (Fig 4). However, the slope of the pressure–cross-sectional area relation did not correlate with either blood pressure or plasma potassium concentrations in either the entire cohort of 48 rats or in each individual group.

Histological Studies

There was no significant difference in media thickness, elastin content, or collagen content of the aortic wall among the three groups. Endothelium was intact and unremarkable in all sections.

Discussion

In the current study of the salt-loaded DS rat, we have confirmed earlier observations that dietary supplementation of potassium attenuates hypertension9,11,13 and preserves EDRF release as measured indirectly from acetylcholine-induced relaxation of precontracted aortic rings. The results of the current study demonstrate that, in this experimental circumstance of potassium supplementation of 3 weeks' duration, the extent to which hypertension is attenuated is directly and...
sured in vitro in thoracic aortic segments. Dietary supplemen-
tation with KCl and KHCO₃ significantly enhanced aortic
compliance.

significantly related to the extent to which EDRF
release is preserved; with supplementation of either
KHCO₃ or KCl, the regression line defining the inverse
relation between blood pressure and EDRF release is
highly significant, and the two lines are not different
from each other. Given that both surgical and pharma-
cological attenuation of hypertension predictably pre-
serve EDRF release in a variety of experimental animal
models of hypertension,6-8,32 it would be difficult to
argue that in the current study attenuation of hyperten-
sion by potassium supplementation did not at least
contribute to the preservation of EDRF release. With
respect to both slope and intercept, the two regression
lines defining the relation between blood pressure and
EDRF release in the rats supplemented with potassium
are not different from that line defining this relation in
rats unsupplemented with potassium. Thus, in the cur-
rent study, the capacity of potassium supplementation
to restrict the salt-induced rise in blood pressure fully
accounts for its capacity to preserve EDRF release,
whatever the mechanism of that restriction.

Preliminary observations have suggested that K⁺ can
increase EDRF release from cultured endothelial cells
in vitro.33 It could be argued that in the current study
supplemental K⁺ directly enhances EDRF release and
thereby restricts an increase in blood pressure, a vari-
able enhancement accounting for the observed inverse
relation between blood pressure and EDRF release.
Clearly, our studies do not exclude this possibility. But
if supplemental K⁺ does induce a variably enhanced
release of EDRF, it cannot be related to the observed
increases in plasma potassium induced by supplemental
potassium in the current study (see below); the extent of
preservation of EDRF release is not related to the
extent of the observed increase in nocturnal plasma K⁺.
Irrespective of whether the enhancement of EDRF
release induced by K⁺ supplementation is either the
result or the cause of the observed attenuation of
hypertension, the enhancement and attenuation would
seem to be causally related.

Raij et al4 have recently concluded that in the DS rat
in which dietary potassium was supplemented for 7
weeks, the capacity of this supplementation to preserve
endothelium-dependent relaxation is independent of its
capacity to attenuate hypertension. But in the current
study of relatively short-term supplementation, had
potassium exerted a preserving effect on EDRF release
independent of its antihypertensive effect, one might
have anticipated some preservation of EDRF release in
at least some of the rats in which potassium supplemen-
tation failed to attenuate hypertension. But such pres-
ervation did not occur. Rather, in each of that minority
of five rats in which potassium supplementation failed
to restrict blood pressure to a value less than 150 mm Hg
(see Fig 3), the extent of impairment in EDRF release
was not different from that in similarly hypertensive rats
unsupplemented with potassium. It might be noted that
in the study of Raij et al in DS rats, preservation of
EDRF release varied inversely with blood pressure,
when data from all three salt-loaded study groups are
considered. We would conclude that in the salt-loaded
DS rat the capacity of supplemental dietary potassium
to preserve EDRF release is not independent of its
capacity to attenuate hypertension, at least after a 3-
week period of such supplementation, when the
supplementation clearly restricts the rise in blood
pressure.

In previous studies of salt-loaded, salt-sensitive hy-
pertensive rats,4,5 including the DS rat,46 it has been
shown that supplemental dietary K⁺ does not affect
endothelium-independent vasorelaxation, as judged
from complete concentration-response curves to so-
dium nitroprusside. Similarly, in the current study,
the greater maximal response to acetylcholine in K⁺-sup-
plemented rats cannot be explained by an endothelium-
independent mechanism (ie, a heightened range of
smooth muscle relaxation), as judged from the maximal
vasodilator response to sodium nitroprusside,34 which
was not greater in the K⁺-supplemented rats and was
greater than 90% in all groups. Thus, in the DS rat that
is salt loaded for 3 weeks, we would conclude that
supplemental dietary K⁺ preserves EDRF release only
to the extent that it restricts the rise in blood pressure.
Raij et al4 demonstrated that dietary K⁺ supplemen-
tation had no effect on EDRF release in the Dahl
salt-resistant (DR) rat and that K⁺ supplementation
in the DS rat was attended by a level of EDRF release not
different from that observed in DR rats. Thus, although
we did not study the DR rat or any other normotensive
control, it seems likely that K⁺ supplementation miti-
gated an otherwise impaired release of EDRF in the
salt-loaded DS rat.

In some studies of the effect of K⁺ supplementation
on blood pressure45 and on endothelial function4,5 in
the DS rat and the SHRSP, it has been reported that
plasma concentrations of K⁺ remained unchanged. It is
therefore contended that the antihypertensive effect of
K⁺ and its preserving effect on the endothelium are
independent of changes in plasma K⁺.4,5 But in those
studies, plasma concentrations of K⁺ appear not to have
been measured at night.4,5,45 Because rats are mainly
nocturnal feeders, one might expect K⁺ supplemen-
tation to induce the greatest increase in plasma concen-
tration of K⁺ at night or early morning. In fact, in the
present study, the diurnal value of the plasma concen-
tration of potassium did not increase, whereas the
nocturnal value increased substantially. The failure of
dietary K⁺ to induce a rise in diurnal plasma K⁺ may be

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Fig 4. Line graph shows estimation of vascular compliance
obtained from pressure–cross-sectional area relation mea-
sured in vitro in thoracic aortic segments. Dietary supplemen-
tion with KCl and KHCO₃ significantly enhanced aortic
compliance.
unique to the Dahl rat. In at least three studies of K+–supplemented Dahl rats, presumably diurnal values of plasma K+ have been reported to be not increased.33,36,38 We are unaware of any studies showing a diurnal increase. By contrast, a presumably diurnal increase in the plasma concentration of potassium has been repeatedly shown in the spontaneously hypertensive rat supplemented with potassium.37,39

In the present study, dietary supplementation of potassium enhanced arterial compliance (compared with unsupplemented rats), an enhancement that could mediate, at least in part, its antihypertensive effect. Many studies have suggested that K+ supplementation reduces systolic blood pressure more than diastolic blood pressure.16-19 Agents such as nitrovasodilators24-40 and angiotensin converting enzyme inhibitors25 that attenuate systolic blood pressure may do so by inducing a relaxing effect on smooth muscle of medium-sized and large arteries that increases their compliance.23,41 Nitrovasodilators induce vasodilation through their metabolism to nitric oxide in vascular smooth muscle.42 Nitric oxide is an important component of EDRF.43-44 Because the present study and those of others3,5 have shown that supplemental dietary K+ preserves the capacity of aortic rings to release EDRF, the vasodilator mechanism of K+ supplementation may be similar to that of nitrovasodilators in large arteries.25 Indeed, because enhanced aortic compliance induced by supplemental K+ could not be related to any obvious structural changes in the aortic media in our study, the enhancement might reflect a decrease in aortic smooth muscle tone caused by supplemental K+.45-48 mediated in part by EDRF. Relaxed vessels are more compliant than contracted vessels, possibly because vascular smooth muscle is in series with collagen elements but in parallel with elastin elements.49 Hence, in the relaxed state, the effects of stretch are transferred to the more distensible elastin elements; supplemental dietary K+ may enhance compliance through a similar mechanism.

Antihypertensive agents that act through mechanisms other than vasorelaxation need not enhance vascular compliance; for instance, diuretic therapy did not reduce aortic stiffness in either a genetic or an experimental rat model of hypertension, despite lowering blood pressure.50 In our study, the extent to which supplemental K+ enhances compliance bears no relation to the measured value of blood pressure. Thus, the observed capacity of K+ to preserve arterial compliance cannot be judged to be a nonspecific effect of attenuation of hypertension. Furthermore, it is possible that the effect of supplemental dietary K+ on arterial compliance could be a chronic/structural effect, which might account for a lack of correlation of compliance with blood pressure that is measured at a single point in time. Such a chronic/structural effect could be distinct from a preserving effect of K+ on endothelial function, which could represent a more dynamic interaction between blood pressure and the vascular endothelium and its release of EDRF.

Supplemental K+ can increase urinary sodium excretion in humans with and without hypertension51-54 and in animals.55-58 Louis et al57 reported that supplemental K+ induced a reduction in exchangeable sodium in spontaneously hypertensive rats. However, Dietz58 and Volpe et al54 concluded that the antihypertensive effect of supplemental K+ could not be related to a reduction in intravascular volume. Avolio et al55 reported that in normotensive subjects dietary salt restriction was attended by a lesser vascular stiffness, as judged from a lower pulse wave velocity. The sodium content of the arterial wall has been reported to be increased in experimental hypertension60; supplemental dietary K+ might decrease vascular stiffness by inducing a decrease in vascular sodium. Although it is possible that a transient natriuresis occurred during the first few days of dietary K+ supplementation in our study, we could not detect either natriuresis or a reduction in body weight (with KHCO3) over the 3-week period of supplementation. Thus, neither a reduction in plasma volume nor tissue sodium can be readily invoked as a mechanism of either the attenuation of hypertension or enhancement of arterial compliance. It therefore remains to be investigated how transient nocturnal increases in plasma K+ as observed in the current study might affect the attenuation of hypertension observed during the day and presumably extant throughout the 24-hour period. In the present study, the increase in urinary K+ excretion induced by supplemental K+ was greater with KHCO3 than with KCl, as was the increase in nocturnal plasma K+, consistent with a greater intestinal absorption of K+ as the bicarbonate salt.

Because the chloride ion has been shown to be important to the hypertensinogenic effect of sodium chloride in salt-sensitive rats,61,62 this anion might constrain the antihypertensive effect of supplemental potassium in the DS rat. However, in the short duration of the present study, the antihypertensive effect of supplemental potassium appeared to be similar in magnitude with either the chloride or bicarbonate salt. It is possible that with longer periods of potassium supplementation, lesser degrees of salt loading, or nocturnal measurements of blood pressure, dissimilar antihypertensive effects might be seen with different potassium salts.

In summary, we have shown that in salt-loaded DS rats, the extent to which supplemental dietary K+ preserves endothelium-dependent relaxation varies directly with the extent to which supplemental K+ restricts the rise in blood pressure, i.e., inversely with directly measured arterial blood pressure. Furthermore, the antihypertensive effect of dietary K+ is associated with an increase in nocturnal but not diurnal plasma K+.

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