Factors Influencing Vascular Hyporesponsiveness to Angiotensin II

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SUMMARY Bartter's syndrome is characterized, in part, by hyporesponsiveness to the pressor effect of exogenous angiotensin II (AI). This has been attributed to volume contraction, hypokalemia, and/or increased prostaglandin (PG) levels. In order to investigate factors responsible for a diminished response to the pressor effect of AI, rats were made hypokalemic or volume contracted and hypokalemic (VCHK) by dietary restriction. AI sensitivity was examined by determining the dose of AI required to raise the mean arterial pressure 20 mm Hg. When compared with control rats, VCHK and hypokalemic rats were significantly less sensitive to AI. VCHK rats were significantly less sensitive to AI than hypokalemic rats. Both experimental groups were similarly hypokalemic, but plasma renin activity (PRA) of VCHK only was greater than control values. In VCHK rats, acute K⁺ restoration partially corrected AI hyporesponsiveness, although plasma K⁺ increased to normal. In VCHK rats, acute volume expansion with normal saline similarly achieved only partial correction of AI hyporesponsiveness although PRA values fell to the control range. Simultaneous K⁺ restoration and volume expansion to VCHK rats successfully restored AI sensitivity to the control range. Dietary sodium, chloride, and potassium restriction did not increase urinary excretion of PGE₂. Indomethacin (5 mg/kg, iv) given acutely to VCHK rats did not significantly alter baseline hyporesponsiveness to AI. Norepinephrine vascular sensitivity was not affected by either volume contraction or hypokalemia. These data demonstrate that volume contraction and hypokalemia individually depress exogenous AI sensitivity in the rat and do so by separate and additive mechanisms. Furthermore, these mechanisms appear to be independent of PG.

A NUMBER of clinical conditions are associated with decreased responsiveness to the pressor effect of AI. Among these are normal pregnancy (Chesley et al., 1963), salt depletion (Ames et al., 1965), psychogenic vomiting (Radfar et al., 1978), cirrhosis (Laragh et al., 1963), the nephrotic syndrome (Johnson and Dose, 1963), renovascular hypertension (Kaplan and Silah, 1964a), adrenal insufficiency (Kuchel et al., 1964), and Bartter's syndrome (Bartter et al., 1962). Several mechanisms have been proposed to explain the resistance to AI that is observed in these conditions. In general, there is an inverse relationship between pressor responsiveness to AI and the state of activation of the renin angiotensin system. It is inferred that in high renin states more vascular receptors are occupied by circulating endogenous AI with proportionately fewer free receptors available to exogenously administered AI (Kaplan and Silah, 1964b). It has also been proposed that chronic elevation AI levels might decrease the avidity of the vascular receptors for AI (Brunner et al., 1972), or might decrease the total number of AI receptors in vascular tissue (Devynck and Meyer, 1976).

Recent investigation of Bartter's syndrome has suggested additional factors which might influence AI responsive. Of particular interest are the observations that endogenous vasodepressor compounds are elevated in this disorder. The spectrum of findings in Bartter's syndrome is now understood to include increased levels of plasma bradykinin, increased urinary kallikrein, and increased urinary excretion of prostaglandin E₂ (PGE₂), in addition to the original description of hypokalemia, hyperreninemia, hyperaldosteronemia, normotension, and striking resistance to the pressor effect of exogenously administered AI (Bartter et al., 1962; Gill et al., 1976; Haluska et al., 1977; Vinci et al., 1978). Despite this more complete characterization, the primary pathophysiology of Bartter's syndrome is still unresolved. Furthermore, understanding the nature of the AI hyporesponsiveness seen in this disorder is complicated by the number of potential contributing factors and by an incomplete understanding of the precise interaction of these factors. For example, hypokalemia is known to cause AI hyporesponsiveness in both the rat (Rosenman et al., 1952) and the dog (Galvez et al., 1977). Although
there is no change in PGE2 excretion in the hypokalemic rat, in the dog, induction of hypokalemia is associated with increased urinary excretion of PGE2, suggesting that hypokalemia might be a primary stimulus for increased PG synthesis (Galvez et al., 1977). PGE2 antagonizes the vasoconstriction produced by either AII or epinephrine (Hedwall et al., 1971; Kadowitz, 1972; Aiken and Vane, 1976). Administration of indomethacin, an inhibitor of PG synthesis, restored AII sensitivity in the previously mentioned hypokalemic dogs (Galvez et al., 1977). Therapeutic intervention with indomethacin in patients with Bartter's syndrome typically only partially corrects hypokalemia. However, a number of the above-mentioned abnormal variables associated with this condition, including AII insensitivity, return toward normal with indomethacin treatment (Gill et al., 1976; Verbeckmoes et al., 1976; Norby et al., 1976; Bowden et al., 1978; Fichman et al., 1976; Richards et al., 1978). Exactly how indomethacin restores vascular responsiveness to AII is unknown. The partial correction of hypokalemia, the decrease in endogenous AII, decreased PG synthesis, and lowering of the extremely potent vasodilator bradykinin might all play a role.

The following experiments were designed to clarify the relative contributions of hypokalemia, salt depletion, and PGE2 to the induction and maintenance of AII hyporesponsiveness.

Methods

Male Sprague-Dawley rats weighing 210-380 g were used throughout this investigation. Control rats had ad libitum access to normal Purina rat chow and tap water. Four groups of rats were volume contracted and made hypokalemic by feeding 15 g/day of a specially prepared sodium, potassium, chloride-free diet (ICN Pharmaceuticals) for approximately 2 weeks allowing ad libitum access to tap water. Another group of rats was made hypokalemic by adding 3 mEq/day NaCl to the above experimental dietary protocol.

On the morning of the experiments, rats were anesthetized with Inactin (100 mg/kg of body weight, ip; BYK) A tracheostomy was placed and polyethylene catheters were inserted in the jugular vein, carotid artery, and the bladder. Venous blood for PRA determination was drawn and replaced with EDTA and immediately spun down and refrigerated. Arterial blood samples were used for all other blood chemistries. Sodium, potassium, chloride, hematocrit, creatinine, and PRA were determined as previously described (Kurtzman, 1970).

So that overnight urine samples for PGE2 assay might be collected, animals were housed in metabolic cages. The urine was collected in ice-jacketed polystyrene beakers then stored without preservative at -20°C until assayed. Aliquots (0.25-ml) of rat urine were acidified to pH 3.0-3.4 with three drops of 0.3 m acetic acid and extracted with chloroform essentially as described by Scherer et al. (1978). The chloroform extracts, evaporated to dryness at 37°C under N2, were stored at -20°C or chromatographed immediately. The recovery of (H) PGE2 added to the urine averaged 96%. The residues from the chloroform extracts were dissolved in a mixture of benzene and ethyl acetate and chromatographed on 1-g silicic acid columns essentially as described by Dunn et al. (1976). Recovery of (H) PGE2 in the PGE2 containing fraction was between 55 and 70% of that applied to the columns. The appropriate fractions were taken to dryness at 37°C under N2 and stored at -20°C until analyzed. Up to 40 columns were run at one time. Residues of the PGE2 containing fractions were dissolved in 1.0 ml of phosphate-buffered saline (pH 7.4) by vortexing vigorously for 15 seconds. Aliquots were diluted generally from one to three with the buffer prior to aliquoting for assay. A 0.5-ml aliquot of each undiluted sample was counted and individual recoveries calculated. The radioimmunoassay utilized rabbit anti-PGE2-albumin antisera (Miles Research Products) and the Miles-Yedda procedure furnished with the antisera.

Indomethacin used in these experiments was prepared fresh daily in 0.1 M phosphate buffer (pH 8.0). The experimental procedure was as follows: After the collection of baseline blood and urine samples, the dose of AII in ng/kg per min which raised the mean arterial pressure by 20 ± 2 mm Hg on two occasions was determined. All sensitivity determinations were made from stable baseline levels of mean arterial pressure. AII was infused with a Sage Instruments pump (model 355), and blood pressure response was determined by carotid manometry using a Statham blood pressure transducer (SP 1400). After the baseline AII sensitivity determinations, acute restoration of the experimental metabolic deficit was achieved according to the following protocols:

Group 1—Volume Expansion in Volume-Contracted Hypokalemic Rats

Six rats prepared according to the volume contraction hypokalemia dietary protocol were studied before and after a 1-hour infusion of 0.9% NaCl in an amount equivalent to 10% of body weight. In six additional rats, 24 hours urine PGE2 levels were measured before and after the above dietary manipulation.

Group 2—Volume Expansion and Potassium Restoration in VCHK Rats

Seven rats prepared according to the VCHK dietary protocol were studied before and 1 hour
after a 1-hour infusion of 0.9% NaCl (10% of body weight) to which was added 6 mEq /KCI per kg rat.

**Group 3—Potassium Restoration in VCHK Rats**

Six rats prepared according to the VCHK dietary protocol were studied before and 1 hour after completion of a 1-hour infusion of 6 mEq KCI/kg rat. The infusion solution was 1 M KCI in order to avoid concomitant volume expansion.

**Group 4—Potassium Restoration in Hypokalemic Rats**

Six rats prepared according to the hypokalemic dietary protocol were studied before and 1 hour after completion of a KCI infusion given as described for group 3.

**Group 5—PG Synthesis Inhibition in VCHK Rats Followed by Volume Expansion**

Six rats prepared according to the VCHK dietary protocol were studied before and 45 minutes after the acute administration of indomethacin (5-10 mg/kg, iv push). These rats were subsequently volume expanded according to the group 1 protocol. After completion of the infusion, a second dose of indomethacin (3 mg/kg, iv push) was administered, and, after a 20-minute wait, blood samples were collected and All responsiveness retested.

**Group 6—Vascular Sensitivity to Norepinephrine**

This group consisted of four control rats, five volume-contracted hypokalemic rats, and four hypokalemic rats. These animals were placed on the dietary protocols as described above and the sensitivity to norepinephrine infusion was studied. Blood was drawn for plasma potassium prior to the infusion. The concentration of norepinephrine required to raise the mean arterial pressure 20 mm Hg was recorded.

**Controls**

Control rats previously fed a normal diet were studied before and after volume expansion as described for group 1.

All mean values have been expressed with the standard error of the mean as the index of dispersion. Tests of statistical significance were made with the paired and nonpaired Student's t-test. The null hypothesis was rejected when a P value of less than 0.05 was achieved.

**Results**

**Group 1—Volume Expansion in VCHK Rats**

The effects of volume expansion on All responsiveness in controls and VCHK rats is shown in Figure 1. Restriction of NaCl and K resulted in a significant increase in hematocrit, in plasma renin activity, and in a decrease in serum K as compared to controls (Table 1). These findings indicate that dietary manipulation produced the expected alterations. At the time of baseline testing, VCHK rats required significantly more All to achieve the desired pressor response than did the control group (98 ± 10 vs. 21 ± 2 ng/kg per min, P < 0.001). After volume expansion, the mean pressor dose of All for VCHK rats fell significantly to 62 ± 10 ng/kg per min (P < 0.01); however, this value is still markedly elevated when compared with the corresponding value for controls (P < 0.01). Volume expansion restored the high baseline PRA levels of group 1 to the control range, but did not alter the low baseline plasma potassium of group 1 (Table 1). Thus correction of volume contraction in VCHK rats only partially restores All responsiveness despite complete normalization of PRA levels.

**Group 2—Volume Expansion and Potassium Restoration in VCHK Rats**

The results of All responsiveness testing for group 2 and all remaining experimental groups is shown in Figure 2. Control values have been repeated for comparison. Simultaneous volume expansion and potassium restoration in VCHK rats resulted in total correction of All hyporesponsiveness (89 ± 7 to 25 ± 3 ng/kg per min, P < 0.001). The mean All pressor dose postinfusion was not significantly different from the baseline control value. In addition to lowering the group 2 PRA levels to the control range (Table 1), the infusion also raised the mean plasma potassium from 2.8 ± 0.1 to 4.8 ± 0.4 mEq/liter, a value significantly higher than that of the control rats. It is unlikely that this relatively minor difference in potassium levels when compared with controls was of critical importance in the restoration of All responsiveness. Group 2 rats responded similarly to the infusion, and there was no correlation between the level of plasma potassium attained postinfusion and the amount of All required to achieve the desired pressor response.

**Group 3—Potassium Restoration in VCHK Rats**

Potassium restoration partially restored All responsiveness in VCHK rats (88 ± 10 to 48 ± 4 ng/kg per min, P < 0.01; Fig. 2). This partial restoration is similar to that described for volume expansion alone. Volume expansion in VCHK rats lowered the required dose of All by a factor of 0.63 whereas potassium restoration lowered the required dose of All by a factor of 0.55. This partial restoration of All responsiveness by KCI infusion does not appear to be dependent on a decrease in endogenous All because postinfusion PRA levels are still three times higher than baseline control values (Table 1).
Thus, with respect to their influence upon All hyporesponsiveness, volume contraction and hypokalemia seem to interact additively but by separate mechanisms.

Group 4—Potassium Restoration in Hypokalemic Rats

At baseline, group 4 rats are hyporesponsive to All (61 ± 6 ng/kg per min; Fig. 2), however the level of insensitivity to All is significantly less than that of all VCHK rats (P < 0.01). KCl infusion, however, does not fully restore All sensitivity to group 4, for the postinfusion All dose (40 ± 3 ng/kg per min) is significantly higher than the mean control dose (P < 0.01). The reason for this failure is unclear, as postinfusion plasma potassium is not significantly different from that of groups 2 and 3, whereas postinfusion PRA levels are not significantly different from baseline control values (Table 2).

<table>
<thead>
<tr>
<th>TABLE 1 Plasma Electrolytes, Hematocrit, and Plasma Renin Activity before and after Volume Expansion and K Replacement in the Different Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group volume expansion</td>
</tr>
<tr>
<td>Na⁺ (mEq/liter)</td>
</tr>
<tr>
<td>P</td>
</tr>
<tr>
<td>Postinfusion</td>
</tr>
<tr>
<td>K⁺ (mEq/liter)</td>
</tr>
<tr>
<td>P</td>
</tr>
<tr>
<td>Postinfusion</td>
</tr>
<tr>
<td>Cl⁻ (mEq/liter)</td>
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<tr>
<td>P</td>
</tr>
<tr>
<td>Postinfusion</td>
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<tr>
<td>Hct (%)</td>
</tr>
<tr>
<td>P</td>
</tr>
<tr>
<td>Postinfusion</td>
</tr>
<tr>
<td>PRA (ng/ml per hr)</td>
</tr>
<tr>
<td>P</td>
</tr>
<tr>
<td>Postinfusion</td>
</tr>
</tbody>
</table>

Preinfusion vs. control postinfusion: P < * 0.06; ** 0.01; *** 0.001. Postinfusion vs. control postinfusion: P < §§ 0.005; §§§ 0.001.
Group 5—PG Synthesis Inhibition in VCHK Rats Followed by Volume Expansion

Previous experiments have shown that hypokalemia alone is associated with AII hyporesponsiveness, and that volume contraction interacts additively with hypokalemia to increase AII hyporesponsiveness. Figure 3 shows that urinary PGE2 excretion was not increased by the dietary protocol for VCHK rats. To investigate further the role of PGE2 in this model of AII hyporesponsiveness, indomethacin was administered acutely to VCHK rats. Inhibition of PG synthesis did not alter baseline hyporesponsiveness to AII (Fig. 2), although PRA levels showed a small but significant drop in post-indomethacin (Table 2). Volume expansion and additional indomethacin failed to normalize AII responsiveness (Fig. 2). These results are not significantly different from volume expansion alone without indomethacin as in group 1 (Fig. 1), and they fail to demonstrate a role for PGE2 in this model of AII hyporesponsiveness.

Group 6—Vascular Sensitivity to Norepinephrine

To ascertain the specificity of the AII unresponsiveness, a separate group of animals was studied for norepinephrine sensitivity. The concentration of norepinephrine required to raise the mean arterial blood pressure 20 mm Hg was 144.5 ± 9.1 mg/kg per min in control rats (n = 5). In VCHK and hypokalemic rats, the concentration of norepinephrine required to produce the same effect was 149.0 ± 11.5 (n = 5) and 131.0 ± 9.1 ng/kg per min, respectively. Both values are not significantly different than the control. Plasma K was 3.7 ± 0.2 mEq/liter in control rats. In VCHK and hypokalemic rats plasma K was 2.7 ± 0.1 and 2.0 ± 0.1 mEq/liter, respectively. Both values are significantly less than control at the 0.05 level.

Discussion

The present study demonstrates that, in the rat, volume contraction and hypokalemia individually

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**Table 2.** Plasma Electrolyte, Hematocrit, and Plasma Renin Activity in Volume-Contracted Hypokalemic Rats during Baseline, Indomethacin, and Saline Administration

<table>
<thead>
<tr>
<th>Volume-contracted, hypokalemic—Group 5</th>
<th>Baseline</th>
<th>Post-indomethacin</th>
<th>Post-volume expansion and indomethacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺ (mEq/liter)</td>
<td>142 ± 3</td>
<td>143 ± 3</td>
<td>145.7 ± 1.8</td>
</tr>
<tr>
<td>K⁺ (mEq/liter)</td>
<td>1.78 ± 1</td>
<td>2.8 ± 0.2</td>
<td>3.0 ± 0.1</td>
</tr>
<tr>
<td>Cl (mEq/liter)</td>
<td>91 ± 3</td>
<td>91 ± 3</td>
<td>194 ± 2**</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>50.8 ± 0.8</td>
<td>&lt;0.01</td>
<td>40.2 ± 0.8***</td>
</tr>
<tr>
<td>PRA (ng/ml per hr)</td>
<td>62.5 ± 2.8</td>
<td>&lt;0.02</td>
<td>23.8 ± 2.8***</td>
</tr>
</tbody>
</table>

Post volume expansion vs. baseline. \( P < ** 0.01, *** 0.001 \)
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Urinary PGE2 in Group 5 Rats on Normal Diet and After 2 Weeks of Na, K, Cl Free Diet (Overnight urine collections)

**Figure 3** Twenty-four-hour prostaglandin E2 excretion (right panel absolute values). Left panel the same data (corrected for mg of creatinine) before and after 2 weeks of Na+, Cl−, K− free diet.

Depress vascular responsiveness to exogenous AII and do so by separate and additive mechanisms. Furthermore, our experiments show that prostaglandins do not contribute to the acute maintenance of AII resistance in the volume-contracted hypokalemia rat. The vascular unresponsiveness is specific for angiotensin in that norepinephrine sensitivity was unaffected by hypokalemia or volume contraction.

Several hypotheses have been proposed to explain the mechanism of AII hyporesponsiveness observed during volume contraction. These include a direct effect of sodium depletion on the contractile response of vascular smooth muscle induced by AII (Ames et al., 1965; Brunner et al., 1972; Strewler et al., 1972), chronic changes in the number (Devynek and Meyer, 1976) or affinity (Brunner et al., 1972) of the vascular receptors for AII, and saturation of these vascular receptors by high levels of circulating endogenous AII (Kaplan and Silah, 1964b). This last explanation is probably the simplest and is supported by the reciprocal relationship generally observed between sensitivity to infused AII and circulating levels of AII. Our findings that acute volume and potassium restoration of VCHK rats normalized AII sensitivity also argues against the primary importance of any chronic alteration in receptor number in the mechanism of AII hyporesponsiveness. The time that elapsed from the start of our infusion to the time of retesting, some 2 hours, is simply too brief an interval for a stimulus to be sensed adequately and for receptors to then be synthesized and made operational.

The present experiments also demonstrate an important role for potassium in AII sensitivity as underscored by the fact that the AII hyporesponsiveness of the VCHK rats could be similarly decreased by either potassium restoration or volume replacement. Indeed, there was no statistical difference in the relative increase of AII sensitivity in VCHK rats following volume expansion alone when compared with that of potassium restoration alone. This would seemingly imply that the AII resistance induced by 2 weeks of sodium chloride and potassium deprivation is not solely the result of either volume contraction or hypokalemia. Rather, one must conclude that volume contraction and hypokalemia are equally important and additive in the expression of maximal AII resistance in the VCHK rat. Although chloride has been shown to be the important ion in the inhibition of plasma renin activity by NaCl (Kotchen et al., 1978), it is obvious that chloride alone cannot be responsible for AII insensitivity in VCHK rats, since KCl or NaCl alone failed to correct the AII insensitivity completely.

The mechanism for the AII hyporesponsiveness associated with hypokalemia is unclear. Although there was a tendency for higher PRA levels in hypokalemic group 4 rats when compared with controls (Table 2), the difference is not statistically significant. Hypokalemia has been felt to be a stimulus for increased renin secretion (Abbrecht and Vander, 1970; Sealy et al., 1970), although this was not demonstrated in the present experiments. The fact that the PRA levels of the VCHK rats fell minimally after KCl infusion (Table 1) despite a significant increase in AII responsiveness argues against activation of the renin angiotensin system by potassium depletion as being of primary importance in the generation of AII resistance.

Despite the strong evidence for the role of potassium in AII hyporesponsiveness, it is interesting to note that hypokalemic rats could not
be restored to the control range of All responsiveness following postassium restoration (Fig. 2). The amount of potassium infused in this group is identical to the amount which, when coupled with volume replacement, fully restored the All responsiveness of the VCHK rats. Although the hypokalemic rats' potassium levels post-KCl infusion are not statistically different from the VCHK rats post infusion, it is possible that the group 4 hypokalemic rats were actually more potassium depleted than the VCHK rats. One would expect that the continual delivery of sodium to the distal renal tubules of rats on restricted potassium diets would lead to a greater exchange of sodium for potassium than would occur in rats who were both sodium chloride and potassium depleted. In the latter group, the proximal reabsorption of sodium would be maximal and thus the distal delivery of sodium to potassium-exchanging sites would be considerably reduced.

The greater potassium excretion in rats on a normal sodium chloride diet would explain the possible presence of more severe potassium depletion in this group than in the volume-contracted rats.

Prostaglandins have been suggested to play a role in the All resistance seen in Bartter's syndrome (Gill et al., 1976; Fichman et al., 1976; Verbeckmoes et al., 1976), psychogenic vomiting (Radfar et al., 1978), and experimentally induced hypokalemia in the dog (Galvez et al., 1977). In humans, however, experimental potassium depletion of moderate degree was associated with All unresponsiveness and with a fall in PGE2 excretion (Düsing et al., 1980).

To investigate the possible role of prostaglandin overproduction in the All hyporesponsiveness seen in our VCHK rats, we measured 24-hour urinary excretion of PGE2 before salt restriction and approximately 2 weeks after the dietary restriction of sodium chloride and potassium. Similar to humans, PGE2 excretion in the rat did not increase over this period (Fig. 3), thus arguing against excessive renal PGE2 production as the mechanism responsible for the All hyporesponsiveness seen in the volume-contracted hypokalemic state. However, these data do not exclude the possibility that other prostaglandins, perhaps synthesized in the vascular wall, may have played a role in the observed All hyporesponsiveness. To investigate this possibility, we performed experiments in which All responsiveness was tested before and after acute systemic inhibition of prostaglandin synthesis by indomethacin administration.

If prostaglandins were important in the acute maintenance of All sensitivity, one would expect that inhibition of prostaglandin synthesis, allowing time for adequate clearance of previously circulating prostaglandins, would at least partially correct All hyporesponsiveness. The technical difficulties of collecting adequate urine intraexperimentally for prostaglandin assay in volume-contracted rats precluded prostaglandin analysis pre- and post-indomethacin administration. However the dose of indomethacin chosen is five times greater than that previously shown to inhibit renal prostaglandin synthetase approximately 5 minutes after administration in the rabbit (Gafni et al., 1978). Furthermore, the dose selected has also been shown to decrease markedly the elevated urinary excretion of PGE2 and PGF2α in surgically stressed rats (Scherer et al., 1978). Thus, if one can assume adequate prostaglandin synthesis inhibition in the present experiments, prostaglandins would seem to have no role in the acute maintenance of All resistance, since indomethacin administration did not alter All responsiveness in the VCHK rats (Fig. 2). This finding is further supported by the observation that the VCHK diet does not increase the 24-hour urinary excretion of PGE2.

The evidence for an involvement of prostaglandins in the expression of All resistance is mostly indirect. In Bartter's syndrome patients, the association of elevated urinary PGE2 with All resistance and the subsequent normalization of both findings following indomethacin administration is always reported after chronic indomethacin therapy. Typically Bartter's syndrome patients treated with indomethacin gain weight and go into positive sodium balance, decrease their urinary excretion of potassium, and normalize their high PRA levels (Gill et al., 1976; Fichman et al., 1976; Norby et al., 1976; Verbeckmoes et al., 1976; Bowden et al., 1978; Richards et al., 1978). Thus, when All sensitivity is tested in these patients, one cannot infer that the return of All responsiveness is due only to prostaglandin synthesis inhibition. Although our results are not directly applicable to the complex metabolic state that exists in the Bartter's syndrome patients, they do establish a model wherein All resistance is prostaglandin independent and is associated with two of the striking findings of Bartter's syndrome, namely hypokalemia and activation of the renin angiotensin system.

In summary, our experiments have demonstrated a model of exogenous All resistance in which sodium chloride and potassium deficits are of comparable importance in the induction and maintenance of vascular hyporesponsiveness to exogenous All. Further studies are needed to elucidate the mechanism of the All hyporesponsiveness associated with hypokalemia in this model. It would seem reasonable to ascribe the major contribution of sodium chloride depletion in All resistance to activation of the renin angiotensin system with subsequent competition between endogenous All and infused All for a limited number of All binding sites in the vascular wall. Finally, prostaglandins have not been shown to participate in the acute maintenance of All hyporesponsiveness in the VCHK rat.
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