Salt Loads Attenuate Potassium-Induced Vasodilation of Forearm Vasculature in Humans

Toshiro Fujita and Yasushi Ito

To evaluate the role of the sodium pump in resistance control in vivo, we studied vascular responses to potassium, which produces vasodilation by the activation of vascular Na⁺,K⁺-ATPase, in normotensive volunteers receiving a high salt diet compared with volume-depleted subjects receiving diuretic treatment. Forearm blood flow was measured by strain-gauge plethysmography during small increments in local concentrations of potassium with intrabrachial arterial infusions of KCl. Infusions of 0.12 and 0.24 mEq/min KCl increased forearm blood flow and decreased forearm vascular resistance in a dose-dependent fashion. But the simultaneous intrabrachial arterial infusion of 2 μg/min ouabain, a Na⁺,K⁺-ATPase inhibitor, could blunt the decremental response of vascular resistance to 0.12 mEq/min KCl. The decrements of vascular resistance with KCl infusions divided by the initial resistance were significantly less with ouabain compared with those without ouabain (43±4% versus 57±3%, p<0.01). This suggests that potassium produces vasodilation by the activation of vascular Na⁺,K⁺-ATPase activity. Similarly, salt loading (180 mEq NaCl for 7 days) after treatment with diuretics could attenuate percent decrements of resistance with KCl infusions (39±3% versus 53±2%, p<0.01), whereas vascular resistance responses to sodium nitroprusside, a nonspecific vasodilator, and to verapamil, a calcium antagonist, did not change with salt loading after volume depletion. Therefore, salt loading could attenuate forearm vascular response to potassium specifically, as did the administration of ouabain. Evidence supports the hypothesis that volume expansion with salt loading increases endogenous ouabainlike Na⁺,K⁺-ATPase inhibitor concentration, which plays a role in not only the control of extracellular fluid but also the regulation of vascular tone during salt loading. (Hypertension 1993;21:772–778)

KEY WORDS • sodium • potassium • ouabain • vascular resistance • blood flow velocity

Accumulating experimental evidence suggests that natriuresis in response to intravascular volume expansion with salt loading is promoted by an endogenous regulation of Na⁺,K⁺-ATPase.¹⁻⁴ the increased endogenous digitalis-like factor in salt-loaded humans and animals.⁵⁻¹¹ Moreover, endogenous Na⁺,K⁺-ATPase inhibitors may be involved in the development of salt-dependent hypertension, possibly through increasing vascular resistance; their levels rise with increased salt intake to promote natriuresis, increased vascular tone being the trade-off for maintenance of sodium balance.¹²⁻¹² Evidence has shown that plasma supernatant from deoxycorticosterone acetate (DOCA)–salt hypertensive rats, a type of volume-dependent hypertension, reduced ouabain-sensitive ⁸⁷Rb uptake by the tail artery⁶⁻⁹ and that the intravenous administration of the digitalis antibody in DOCA-salt hypertensive rats markedly decreased blood pressure.¹³ Recently, several investigators demonstrated that salt loading in hypertensive patients provoked an increase in Na⁺,K⁺-ATPase inhibitory activity, which was positively related to the increase in mean blood pressure, possibly through increased peripheral vascular resistance.¹⁴⁻¹⁵ There is also the possibility that endogenous Na⁺,K⁺-ATPase inhibitors might be involved in not only the maintenance of sodium balance but also the regulation of vascular tone during salt loading in humans. However, there are very few in vivo studies about the role of endogenous Na⁺,K⁺-ATPase inhibitors in the control of vascular tone during salt loading in humans.

The measurement of forearm vascular response to small increments in local concentrations of potassium with intra-arterial infusion of potassium chloride offers a means of addressing the issue of vascular function in vivo and the role of the sodium pump in the control of vascular resistance,¹⁶⁻¹⁸ because potassium produces vasodilation by the activation of vascular Na⁺,K⁺-ATPase.¹⁹⁻²⁰ If endogenous Na⁺,K⁺-ATPase inhibitor or inhibitors were increased during a high sodium diet, it would be predicted that the vasodilator response to potassium should be reduced in salt-loaded subjects. Therefore, we measured the incremental response of forearm blood flow (FBF) to intra-arterial infusion of potassium chloride under the volume-depleted state with the treatment of diuretics and the volume-expanded state with salt loading. Moreover, we studied the effect of the simultaneous infusion of ouabain on forearm vascular response to K⁺, because Mathews et al recently reported the identification of the endogenous Na⁺,K⁺-ATPase inhibitor as ouabain. In the present study, salt loading, as well as the administration of ouabain, specifically attenuated the vascular response to K⁺ infused into the forearm artery, providing indirect in vivo evidence for the release of endogenous ouabainlike
inhibitors with salt loads and indicating that the sodium pump may be involved in the link between sodium balance and vascular function in humans.

Methods

All 23 subjects (three women, 20 men) were healthy, young (18–24 years) volunteers. Written informed consent was obtained from each subject. Studies were done with subjects in the supine position in an air-conditioned laboratory. A brachial artery was cannulated with a 20-gauge intravenous over-the-needle Teflon catheter for drug infusions. The arterial line was kept open by infusion of heparinized 5% dextrose before drug infusion, and then drugs dissolved in 5% dextrose were infused with a syringe driver (Harvard Apparatus, South Natick, Mass.) at the rate of 0.5–1.2 mL/min. The ipsilateral antecubital vein was also cannulated with 19-gauge hypodermic needles with attached plastic tubing for blood sampling. After placement of two canulas and a strain-gauge plethysmograph and with the subject comfortable in the supine position and the arms supported at a 45° angle from the long axis of the body, at least 15 minutes were allowed for subjects to become accustomed to the study conditions before the protocol was begun.

We measured FBF by a plethysmographic technique, as described previously.17,22 Briefly, changes in forearm blood volume were determined by means of a mercury-in-rubber strain-gauge plethysmograph placed on the midforearm. To eliminate the vessels in the hand from these determinations, we placed a sphygmomanometric cuff 7 cm wide around the wrist and inflated it to a level exceeding systolic arterial pressure just before each venous occlusion. A sphygmomanometric cuff 13 cm wide was placed around the upper arm, and forearm venous occlusion was produced by suddenly inflating this cuff to a pressure below the diastolic arterial pressure (40 mm Hg),23 using a tank of compressed air to provide a constant pressure source. FBF was taken as the average of four to eight flow measurements made at 15-second intervals. Calculation of FBF was done independently and blindly by two of the authors from the copied records, and the average value was used for statistical analysis. Blood pressure was measured in each subject’s other arm with a sphygmomanometer every 1 minute. Diastolic pressure was taken at phase IV of the Korotkoff sounds. FBF (milliliters per 100 milliliters of forearm volume per minute) was calculated from changes in forearm circumference during venous occlusion. Forearm vascular resistance (FVR) was calculated by dividing mean arterial pressure (diastolic pressure plus one third of the pulse pressure in millimeters of mercury) by FBF (milliliters per 100 milliliters of forearm volume per minute); these values are expressed as units throughout this report.

Experimental Protocols

Study A: Forearm blood flow response to KCl infusion.

Seven normotensive subjects were studied. After catheters and a strain-gauge plethysmograph were placed, at least 15 minutes were allowed for each subject to become accustomed to the study conditions before the protocol was begun. The control solution was 5% dextrose; the experimental solution contained 0.15 mEq/mL KCl and was isotonic. With the subject comfortable in the supine position, control solution was infused for 10 minutes, followed by infusions of solution containing KCl delivered into brachial arterial blood at increasing rates of 0.12 and 0.24 mEq/min, each for 10 minutes. Volume infusion rates were 0.8 and 1.6 mL/min, respectively. During the last 2 minutes of each infusion, FBF was measured by continuous arterial blood flow plethysmography. Immediately before the KCl infusion and at the end of each infusion, we simultaneously sampled the ipsilateral and contralateral venous blood for measurement of plasma sodium and potassium concentrations.

Study B: Effects of local ouabain infusion on forearm blood flow responses to KCl and verapamil. Six normotensive subjects were studied. To examine the effect of ouabain on K+-induced vasodilation, we studied FBF responses to KCl with and without the simultaneous infusion of ouabain into brachial arterial blood at a rate of 2 μg/min and compared them with those to verapamil with and without ouabain. After infusion of control solution, KCl was infused into brachial arterial blood at a rate of 0.12 mEq/min for 10 minutes. Subsequently, control solution was again infused for 10 minutes, and then the solution containing verapamil was infused into brachial arterial blood at a rate of 5 μg/min for 10 minutes. Thereafter, the control solution was again infused for 10 minutes, and then the solution containing 2 μg/min ouabain was infused into brachial arterial blood for 20 minutes, followed by the mixed solution containing 2 μg/min ouabain and 0.12 mEq/min KCl for 10 minutes. Subsequently, 2 μg/min ouabain was again infused for 10 minutes, followed by infusions of the mixed solution containing 2 μg/min ouabain and 5 μg/min verapamil for 10 minutes. At each infusion, FBF was measured in the experimental arm. The effect of each infusion of KCl or verapamil was compared with forearm hemodynamics measured during a preceding paired infusion of control or ouabain solution.

Study C: Effects of volume depletion and volume expansion on forearm blood flow responses to KCl, verapamil, and sodium nitroprusside. Ten normotensive subjects were studied on an outpatient basis. Each subject maintained regular customary diets throughout the study. Forearm vascular responses to KCl, verapamil, and sodium nitroprusside were studied after sodium depletion with the administration of a diuretic (25 mg/day mefruside) for 7 days ("diuretic treatment"), and subsequently after 180 mEq sodium chloride each day was added as 10 mEq sodium chloride tablets for 7 days ("high sodium diet"). The aim was to maintain a constant sodium and potassium intake without altering caloric intake. At every visit throughout the trial, subjects brought with them two complete 24-hour urine samples for the determination of sodium, potassium, and creatinine levels. Body weight was recorded at each visit. At the end of the diuretic period and of salt loading, blood for measurements of plasma sodium, potassium, and creatinine concentrations and plasma renin activity was drawn, and FBF responses to KCl, verapamil, and sodium nitroprusside were studied. The control solution was infused for 10 minutes, followed by the infusion of the solution that contained KCl delivered at 0.12 mEq/min into brachial arterial blood. After the infusion of this solution, control solution was again infused for 10 minutes, and then the solution containing

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verapamil was infused at a rate of 5 µg/min for 10 minutes. Thereafter, the control solution was infused for 10 minutes, followed by infusion of the solution containing sodium nitroprusside delivered at 1 µg/min into brachial arterial blood for 10 minutes. At each infusion, FBF was measured in the experimental arm. The effect of KCl, verapamil, and sodium nitroprusside infusions was compared with hemodynamics measured during a preceding paired infusion.

Plasma and urine sodium and potassium concentrations were measured with a flame photometer, and plasma creatinine was measured by an autoanalyzer method. Radioimmunoassay was used to assay plasma renin activity.

### Statistical Analysis

All data are expressed as mean±SEM. One-way analysis of variance was used to test for significant changes in forearm vascular responses to 0.12 and 0.24 mEq/min KCl. Two-way analysis of variance was used to compare the changes in FBF and FVR with KCl, verapamil, and sodium nitroprusside before and after salt loading as well as changes in FBF and FVR with KCl and verapamil before and after ouabain infusion. When analysis of variance was significant, the location of difference was determined by paired or unpaired t test. Regression analysis was performed according to standard procedures. Analysis of covariance was used to compare the differences in the magnitude of KCl response adjusted for differences in initial vascular resistance among subjects on a normal sodium diet and salt-loaded and diuretic-treated subjects. Changes were reported as significant at a value of p<0.05.

### Results

#### Forearm Vascular Response to KCl Infusion

Neither control nor experimental infusions had significant effects on both systemic blood pressure and heart rate in normotensive subjects. Infusions of 0.12 and 0.24 mEq/min KCl increased FBF from 2.03±0.21 to 4.17±0.46 (p<0.01) and 7.05±0.62 mL/100 mL per minute (p<0.01), respectively. Percent increments of FBF to KCl infusion were 113±22% and 262±39%, respectively. Accordingly, KCl infusions decreased FVR from 42.7±5.0 to 17.5±1.3 (p<0.01) and 11.2±1.0 units (p<0.01), respectively. Percent decrements of FVR to KCl infusions were 57±3% and 73±1%, respectively.

Concomitantly, ipsilateral venous plasma potassium concentrations increased from 4.2±0.1 to 5.5±0.1 and 6.8±0.1 mEq/L, without significant changes in contralateral venous plasma potassium concentration (from 4.2±0.3 to 4.3±0.2 and 4.3±0.3 mEq/L). Overall, there was a positive linear correlation (r=0.898, p<0.001) between ipsilateral venous plasma potassium concentrations and FBF during intrabrachial arterial infusions of KCl (Figure 1). Moreover, there were highly linear correlations of initial vascular resistance to magnitude of response to 0.12 mEq/min (r=0.973, p<0.001) and 0.24 mEq/min (r=0.941, p<0.001) KCl infusions.

#### Effects of Local Ouabain Infusion on Forearm Vascular Responses to KCl and Verapamil

Forearm hemodynamic effects of the intrabrachial arterial infusions of KCl and verapamil are presented in Figure 1. Scatterplot shows positive linear correlation between ipsilateral venous plasma concentrations and forearm blood flow during intrabrachial infusions of KCl (r=0.898, p<0.001).

Table 1. Neither control nor experimental infusions had significant effects on systemic blood pressure or heart rate in the subjects studied. Infusions of 0.12 mEq/min KCl increased FBF from 1.98±0.17 to 4.58±0.40 mL/100 mL per minute. However, the simultaneous infusion of ouabain and KCl increased FBF from 1.66±0.14 to only 3.04±0.34 mL/100 mL per minute. FBF during KCl infusion was apparently decreased with the simultaneous infusion of ouabain (3.04±0.34 versus 4.58±0.40 mL/100 mL per minute, p<0.05). Therefore, percent increments of FBF to KCl were significantly less with the simultaneous infusion of ouabain compared with those without ouabain (84±19% versus 139±32%, p<0.01 by paired t test).

Infusions of 0.12 mEq/min KCl decreased FVR from 40.9±2.0 to 17.3±0.6 units (p<0.01). With the infusion of ouabain, basal FVR significantly increased (48.8±3.2 versus 40.9±2.0 units, p<0.01), with an associated decrease in FBF (1.66±0.14 versus 1.98±0.17 mL/100 mL per minute, p<0.05). Subsequently, infusions of KCl decreased FVR from 48.8±3.2 to only 27.3±1.9 units (p<0.01). Thus, the decrements of FVR with KCl infusions were significantly less during the simultaneous infusion of ouabain compared with those before ouabain (43±4% versus 57±3%, p<0.01 by paired t test) (Figure 2), suggesting that ouabain might blunt the FVR response to KCl. In contrast, percent decrements of FVR to the infusion of 5 µg/min verapamil did not differ between those with and without the simultaneous infusion of ouabain (43±4% versus 42±3%, respectively; NS). Thus, local infusion of ouabain blunted the forearm vascular response to KCl but did not affect the response to verapamil.

#### Effects of Salt Loading on Forearm Vascular Responses to KCl, Verapamil, and Sodium Nitroprusside

Table 2 summarizes laboratory findings in 10 normotensive subjects with the diuretic treatment and subsequent salt loading. Body weight increased from 65.2±1.8 to 66.5±1.6 kg (p<0.01) with salt loading; heart rate decreased from 67.5±1.2 to 63.5±1.5 beats per minute (p<0.01). Mean blood pressure remained unchanged (Table 3). Plasma renin activity was signifi-
TABLE 1. Effects of Ouabain on Systemic Hemodynamic and Forearm Blood Flow Responses to KCl and Verapamil in Six Normotensive Subjects

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control 1</th>
<th>KCl</th>
<th>Control 2</th>
<th>Verapamil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>79.2±2.4</td>
<td>79.0±3.0</td>
<td>79.1±2.4</td>
<td>78.8±2.1</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>64±3</td>
<td>64±2</td>
<td>63±2</td>
<td>62±2</td>
</tr>
<tr>
<td>Forearm blood flow [(mL/100 mL)/min]</td>
<td>1.98±0.17</td>
<td>4.58±0.40*</td>
<td>2.08±0.22</td>
<td>3.60±0.41*</td>
</tr>
<tr>
<td>ΔForearm blood flow (%)</td>
<td>139±32</td>
<td>74±12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forearm vascular resistance (units)</td>
<td>40.9±2.0</td>
<td>17.3±0.6*</td>
<td>39.6±2.2</td>
<td>22.9±7.2*</td>
</tr>
<tr>
<td>ΔForearm vascular resistance (%)</td>
<td>57±3</td>
<td>42±3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

With ouabain

| Mean blood pressure (mm Hg) | 78.5±2.6 | 78.4±2.3 | 78.8±2.4 | 78.3±2.5 |
| Heart rate (bpm) | 63±2 | 62±3 | 62±2 | 62±2 |
| Forearm blood flow [(mL/100 mL)/min] | 1.66±0.14† | 3.04±0.34** | 1.84±0.20† | 3.19±0.19* |
| ΔForearm blood flow (%) | 84±19† | 79±11 |
| Forearm vascular resistance (units) | 48.8±3.2† | 27.3±1.9* | 45.6±4.0† | 25.3±1.2* |
| ΔForearm vascular resistance (%) | 43±4† | 43±4 |

bpm, Beats per minute. Control 1 and Control 2, during infusion of 5% dextrose; KCl, during infusion of 0.12 mEq/min KCl; verapamil, during infusion of 5 μg/min verapamil. Values are mean±SEM.
* p<0.01 vs. value of each control solution.
† p<0.05 vs. value during each infusion without ouabain.

Table 2. Laboratory Data in 10 Normotensive Subjects With Diuretic Treatment and Salt Loading

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Diuretic</th>
<th>Salt loading</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>65.2±1.8</td>
<td>66.5±1.6*</td>
</tr>
<tr>
<td>Plasma sodium (mEq/L)</td>
<td>138±1</td>
<td>137±1</td>
</tr>
<tr>
<td>Plasma potassium (mEq/L)</td>
<td>4.2±0.1</td>
<td>4.1±0.2</td>
</tr>
<tr>
<td>Plasma creatinine (mg/dL)</td>
<td>1.0±0.1</td>
<td>1.0±0.1</td>
</tr>
<tr>
<td>Plasma renin activity ([ng/mL]/hr)</td>
<td>3.8±0.2</td>
<td>0.9±0.1*</td>
</tr>
<tr>
<td>Urinary sodium (mEq/day)</td>
<td>223±20</td>
<td>394±25*</td>
</tr>
<tr>
<td>Urinary potassium (mEq/day)</td>
<td>58±6</td>
<td>56±5</td>
</tr>
</tbody>
</table>

Diuretic, at the end of diuretic treatment; salt loading, at the end of salt loading. Values are mean±SEM.
* p<0.01 vs. value of diuretic treatment.
TABLE 3. Effects of Salt Loading on Systemic Hemodynamic and Forearm Blood Flow Responses to KCl, Verapamil, and Nitroprusside in 10 Normotensive Subjects

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control 1</th>
<th>KCl</th>
<th>Verapamil</th>
<th>Control 3</th>
<th>Nitroprusside</th>
</tr>
</thead>
<tbody>
<tr>
<td>During diuretic treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>79.8±3.2</td>
<td>79.8±2.4</td>
<td>79.0±2.5</td>
<td>79.2±2.6</td>
<td>79.0±2.7</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>67.5±1.2</td>
<td>67.3±1.5</td>
<td>67.0±1.8</td>
<td>67.2±1.6</td>
<td>67.2±1.4</td>
</tr>
<tr>
<td>Forearm blood flow ([mL/100 mL]/min)</td>
<td>2.47±0.22</td>
<td>5.13±0.53*</td>
<td>2.89±0.31</td>
<td>5.12±0.48*</td>
<td>2.98±0.32</td>
</tr>
<tr>
<td>ΔForearm blood flow (%)</td>
<td>109±14</td>
<td>70±5</td>
<td>86±12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forearm vascular resistance (units)</td>
<td>35.3±2.9</td>
<td>17.0±1.0*</td>
<td>29.2±4.0</td>
<td>17.3±2.4*</td>
<td>30.2±2.4</td>
</tr>
<tr>
<td>ΔForearm vascular resistance (%)</td>
<td>53±2</td>
<td>38±2</td>
<td>46±3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>During salt loading</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>80.5±2.3</td>
<td>80.4±1.8</td>
<td>80.2±2.0</td>
<td>80.3±2.6</td>
<td>80.1±2.6</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>63.5±1.5†</td>
<td>63.3±1.6</td>
<td>63.2±1.5</td>
<td>63.3±1.8</td>
<td>63.2±1.7</td>
</tr>
<tr>
<td>Forearm blood flow ([mL/100 mL]/min)</td>
<td>2.93±0.27†</td>
<td>5.06±0.54*</td>
<td>3.15±0.29†</td>
<td>5.77±0.57*</td>
<td>3.38±0.22†</td>
</tr>
<tr>
<td>ΔForearm blood flow (%)</td>
<td>73±9†</td>
<td>76±12</td>
<td>80±14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forearm vascular resistance (units)</td>
<td>29.7±1.5†</td>
<td>17.9±0.9*</td>
<td>27.5±1.8</td>
<td>16.2±2.4*</td>
<td>27.0±1.8</td>
</tr>
<tr>
<td>ΔForearm vascular resistance (%)</td>
<td>39±3†</td>
<td>41±4</td>
<td>42±4</td>
<td></td>
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</tr>
</tbody>
</table>

bpm, beats per minute. Control 1, Control 2, and Control 3, during infusion of 5% dextrose; KCl, during infusion of 0.12 mEq/min KCl; verapamil, during infusion of 5 /ig/min verapamil; nitroprusside, during infusion of 1 μg/min nitroprusside. Values are mean±SEM.

*p<0.01 vs. value of each control solution.
†p<0.05 vs. value of diuretic treatment.

points in the control subjects on the normal sodium diet, although the response points to KCl in all 10 diuretic-treated subjects fall within the 95% confidence interval. Moreover, with analysis of covariance, there are significant differences in the magnitude of KCl response adjusted for initial resistance in 10 salt-loaded subjects compared with those in the diuretic-treated subjects (p<0.01) and the subjects on a normal sodium diet (p<0.01). This suggests that salt loading could attenuate vasodilator responses of K⁺.

To consider baseline FBF, we divided these 10 subjects into two groups according to the response of baseline FBF to salt loading: Four of them (group A) had an apparent increase in FBF with salt loading (from 2.37±0.52 to 3.54±0.54 mL/100 mL per minute, p<0.01), and six of them (group B) had no increases in FBF with salt loading (from 2.54±0.20 to 2.52±0.14 mL/100 mL per minute, NS). Salt loading could attenuate the responses of FBF to KCl in both group A and B (79±6% versus 107±11%, p<0.05 by unpaired t test, and 70±14% versus 112±26%, p<0.05, respectively) and the responses of FVR to KCl (41±2% versus 51±3%, p<0.05, and 39±5% versus 52±4%, p<0.05, respectively).

In contrast to KCl responses, there were no significant differences in percent decrements of FVR to infusions of verapamil between the diuretic period and the high sodium diet (38±4% and 41±4%, respectively, NS). FVR response to sodium nitroprusside did not differ between the diuretic period and the high sodium diet (46±3% and 42±4%, respectively, NS). Therefore, it appears that salt loading blunts K⁺-induced vasodilation specifically.

**Discussion**

The first observation, in keeping with previous studies,16-18 is that local arterial infusion of KCl increased FBF in a dose-dependent fashion. It appears that...
potassium elicits a concentration-dependent vasodilation in forearm vascular beds, because there was a positive correlation between ipsilateral venous plasma potassium concentrations and FBF levels during intrabrachial arterial infusions of KCl. It is suggested, moreover, that the mechanism for K+-induced vasodilation is mainly due to the activity of vascular Na+,K+-ATPase, because in the present study the incremental FBF response to intrabrachial arterial infusions of KCl was significantly attenuated by the simultaneous infusion of ouabain, a Na+,K+-ATPase inhibitor. Correspondingly, Kramer et al demonstrated that high dietary potassium intake attenuated the vasoconstrictor effect of ouabain in humans.

It should be noted that in the present study the intrabrachial arterial infusion of ouabain not only could attenuate forearm vascular response to KCl but also could increase basal FVR levels, suggesting that ouabain per se caused vasoconstriction in forearm vascular beds. The results of the present study are consistent with those of several investigators who observed an increase in vascular resistance after infusion of ouabain into the forearm arterial blood in both normotensive volunteers and hypertensive patients. Ouabain-induced vasoconstriction might occur because a Na+,K+-pump inhibitor has the potential for increasing contractile activity by direct and indirect mechanisms. The potential direct mechanisms are either depolarization of muscle cells, leading to increased calcium influx through voltage-dependent calcium channels, or altered sodium–calcium exchange, leading to decreased calcium efflux. Because ouabain would have caused more depolarization and opened more calcium channels, we would have expected that ouabain could modulate the response to verapamil, a calcium channel blocker. In the current study, however, ouabain did not affect the response to verapamil, as in the previous study of Robinson et al. Therefore, the indirect implication from these data is that some other transport pathway for calcium, i.e., sodium–calcium exchange, is involved in the control of vascular tone by the sodium pump. This implication is supported by the recent experiment indicating that incubation of resistance arteries in ouabain to inhibit active sodium influx increases the contractile response to caffeine stimulation by inhibition of sodium–calcium exchange activity.

The most important finding of the present study is that salt loading could blunt the decremental FVR response to the intrabrachial arterial infusion of KCl specifically. Although the precise mechanism for salt-induced attenuation of a K+-induced vasodilator effect is still unknown, we can speculate that salt loading either inhibited directly vascular Na+,K+-ATPase activity in peripheral arterioles or increased some factor or factors due to the activity of inhibitors as ouabain. Moreover, several investigators have demonstrated that salt loading increased plasma and urinary concentrations of circulating ouabainlike factors measured not only by the inhibitory effect of [3H]ouabain binding on human erythrocyte but also by the method using ouabain-sensitive 42Rb uptake by rat tail artery. In addition, purified inhibitors increased intracellular calcium concentrations in cultured smooth muscle cells. Therefore, salt-induced attenuation of K+-vasodilation might be attributable to the increased activity of the endogenous ouabainlike Na+,K+-ATPase inhibitors with salt loads by competing K+-induced activation of vascular Na+,K+-ATPase.

In the present study, salt loading increased basal FBF levels, implying vasodilation rather than vasoconstriction in forearm vascular beds. This is consistent with the result of Abboud’s study indicating that salt loading increased FBF in normotensive humans, possibly by a compensatory response to the increased central blood volume through cardiopulmonary reflex. The apparent increase in blood flow with salt loads might be due to the increased blood volume and cardiac output.

To account for the observation that salt loading attenuated forearm vascular response to K+, one should consider that this is simply related to initial vascular resistance; i.e., the blood vessels are already dilated with salt loading and thus dilate less in response to the second KCl challenge, because there was a significant positive linear correlation between the level of initial FVR and magnitude of forearm vascular response to KCl infusions, as in the response to the other vasodilator agents. Alternatively, salt-induced attenuation of K+-response might be attributable to dilution of infused K+, because salt loading itself increased baseline FBF. However, it should not be attributed to the increased blood flow nor the decreased initial resistance, because in the present study the K+-response was expressed by percent changes to consider initial resistance.

The evidence does not support such a suggestion, because even in six of 10 subjects who had no increases in FBF (group B), salt loading could attenuate the K+-responses in FBF (70±14% versus 112±26%, p<0.05) and FVR (39±5% versus 52±4%, p<0.05). Finally, there was no evidence for blunted vasodilator responses to the other vasodilator agents (sodium nitroprusside and a calcium antagonist) in salt-loaded subjects using the same techniques and methods of analysis, indicating that salt loading blunted the vascular response to K+ specifically. This led us to the hypothesis that salt loading increases endogenous ouabainlike substances. However, there is some possibility that the attenuation is related to salt-induced changes in the K+ metabolism in vascular smooth muscle cells or structural changes of the small vessels, limiting diffusion of K+ but not of verapamil or sodium nitroprusside.

In the present study, salt loading attenuated K+-induced vasodilation in the forearm vascular bed in normotensive young humans, suggesting the release of a humoral ouabainlike substance with functional effects on the resistance arteries.

Acknowledgment
We gratefully acknowledge the secretarial assistance of Kana Nakajima.

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Salt loads attenuate potassium-induced vasodilation of forearm vasculature in humans.
T Fujita and Y Ito

Hypertension. 1993;21:772-778
doi: 10.1161/01.HYP.21.6.772

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1993 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

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