Loss of Sodium Modulation of Plasma Kinins in Human Hypertension

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ABSTRACT
We studied the effect of salt intake and hypertension on the systemic kallikrein-kinin system (KKS), as measured by bradykinin (BK) 1–5, a stable circulating bradykinin metabolite, and the tissue KKS, as measured by urinary kallikrein excretion. Venous BK 1–5, urinary kallikrein, and components of the renin-angiotensin-aldosterone system were measured in 35 normotensive and 19 hypertensive subjects who were maintained on a high (200 mmol/day) or low (10 mmol/day) salt diet. Salt restriction decreased mean arterial pressure (MAP) (P < 0.001 overall) and the plasma angiotensin-converting enzyme (P = 0.017) and increased plasma renin activity (P < 0.001) and serum aldosterone (P < 0.001). There was an interactive effect of salt intake and hypertension on plasma BK 1–5 (P = 0.043), with BK 1–5 significantly lower during low compared with high salt intake in normotensive (24.7 ± 2.6 versus 34.9 ± 5.6 fmol/ml, P = 0.002) but not hypertensive subjects (30.6 ± 4.6 versus 27.5 ± 2.8 fmol/ml, P = 0.335). In normotensives, the change in plasma BK 1–5 from high to low salt intake correlated with the change in MAP (r = 0.533, P = 0.004). Urinary kallikrein was higher during low compared with high salt intake (P < 0.001) in both groups. There was no effect of salt intake on urinary BK 1–5. In summary, the systemic and renal KKSs act in tandem to modulate the response to salt intake. The systemic system is activated during high salt intake and counterbalances increased vascular response to pressors. With sodium restriction, the renal system is activated and counterbalances the increased sodium-retaining state induced by activation of the renin-angiotensin-aldosterone system. With hypertension, these modulating effects are diminished or lost, supporting a role for both systems in the development/maintenance of hypertension.

Bradykinin is a vasoactive peptide that causes vasodilation (Bhoola et al., 1992) and contributes to the blood pressure lowering effects of the angiotensin-converting enzyme (ACE) inhibitors (Gainer et al., 1998; Squire et al., 2000). In recent years, studies using bradykinin receptor antagonists and mice lacking the gene encoding for the bradykinin B2 receptor have elucidated a role for bradykinin in the regulation of blood pressure. These studies suggest that endogenous bradykinin does not play an important role in regulating blood pressure under basal conditions, but bradykinin attenuates the hypertensive effects of high salt intake, mineralocorticoids, and vasoconstrictors such as angiotensin II (Madeddu et al., 1993, 1994, 1998; Cervenka et al., 1999). However, other investigators have reported no effect of bradykinin on salt-sensitive hypertension (Rhaleb et al., 1999; Milia et al., 2001).

Characterizing the role of bradykinin in the regulation of blood pressure in humans has been complicated by three factors. First, there has been a lack of long-acting B2 receptor antagonists for administration to humans. Although studies using short-acting peptide B2 receptor antagonists indicate that endogenous bradykinin contributes to the vasodilator or hypotensive effects of ACE inhibitors (Hornig et al., 1997; Gainer et al., 1998; Squire et al., 2000), these acute studies suggest that endogenous bradykinin does not contribute significantly to blood pressure regulation under basal conditions. On the other hand, as in animals, bradykinin may attenuate the hypertensive effects of vasoconstrictors in humans (Murphey et al., 2000b).

Second, delineating the role of bradykinin in sodium homeostasis and blood pressure regulation in humans has been further complicated by technical difficulties in accurately measuring plasma bradykinin. Although current assays for measuring bradykinin are both sensitive and specific
(Nussberger et al., 1998; Duncan et al., 2000), low circulating concentrations of bradykinin in the presence of substantial concentrations of its precursor and both generating and degrading enzymes can lead to artifactual production during blood sampling. Thus, reported normal bradykinin plasma concentrations have varied over several orders of magnitude (Pellacani et al., 1992).

Third, there are systemic and renal kallikrein-kinin systems. Both could theoretically be involved in blood pressure regulation but via potentially different mechanisms. Many investigators have reported that urinary kallikrein excretion is increased during salt restriction (Margolius et al., 1974; Levy et al., 1977; Hilgenfeldt et al., 1998). This effect of salt restriction on urinary kallikrein excretion is attenuated in subjects with essential hypertension compared with normotensive subjects (Margolius et al., 1971; Levy et al., 1977) and in black Americans compared with white Americans (Levy et al., 1977). However, the measurement of urinary kallikrein reflects the activity of the renal kallikrein-kinin system and not the activity of the systemic or circulating kallikrein-kinin system. Hilgenfeldt et al. (1998) reported that, whereas urinary kallikrein excretion is increased, plasma kallikrein and bradykinin are decreased during salt restriction compared with salt repletion in healthy volunteers. The investigators did not report the effect of salt intake on plasma bradykinin concentrations in hypertensive subjects, and the bradykinin concentrations were higher than those reported by other groups (Nussberger et al., 1998; Duncan et al., 2000). In contrast, Wong et al. (1975) reported that plasma bradykinin levels fell during an acute salt load in parallel with the reduction in plasma renin activity, angiotensin II, and aldosterone.

We have recently identified the bradykinin fragment BK 1–5 (Arg-Pro-Pro-Gly-Phe) as a stable circulating metabolite in humans (Murphey et al., 2000a). Whereas bradykinin has a half-life of seconds, the half-life of BK 1–5 is minutes. BK 1–5 can be measured by using an accurate and precise liquid chromatography-mass spectrometry method. Circulating concentrations of BK 1–5 reflect systemic doses of exogenous bradykinin (Murphey et al., 2000a), and changes in plasma BK 1–5 concentrations reflect changes in the activity of the endogenous plasma kallikrein-kinin system (Sugimoto et al., 1998). The purpose of this study was to examine the effect of salt intake on plasma concentrations of the stable bradykinin metabolite BK 1–5 in normotensive and hypertensive subjects and contrast changes in its levels with changes in the activity of the renin-angiotensin-aldosterone system (RAAS) and urinary kallikrein.

Materials and Methods

Human Subjects. Thirty-five normotensive and 19 hypertensive subjects were studied. The protocol was approved by the Vanderbilt University Institutional Review Board and conducted according to institutional guidelines. All subjects gave written, informed consent. Each subject underwent a screening history, physical examination, laboratory analysis, and ECG. Subjects were defined as normotensive if they had a seated blood pressure <140/90 mm Hg and as hypertensive if they had a seated blood pressure >145/95 mm Hg on three occasions. Except for hypertension, all subjects were healthy. Persons with secondary forms of hypertension were excluded. All antihypertensive medications were discontinued for three weeks before the study, and during the study subjects took no medications.

General Protocol. Subjects participated in ongoing studies of the effects of salt intake on responses to angiotensin II infusion (Shoback et al., 1983). Briefly, subjects were supplied a caffeine- and alcohol-free diet that consisted of a daily intake of 200 mmol of sodium (high salt), 100 mmol of potassium, 500 mg of calcium, and 200 to 300 mg of carbohydrates for 7 days. Beginning on the 7th day, subjects were asked to collect all of their urine for 24 h for measurement of sodium, potassium, kallikrein, and BK 1–5. On the morning of day 8, subjects reported fasting to the Vanderbilt General Clinical Research Center. After 1 h in the supine position, para-aminohippurate was infused for measurement of renal plasma flow. One hour later, blood was drawn for measurement of BK 1–5, plasma renin activity (PRA), aldosterone, and plasma ACE activity. Subjects underwent phenotyping for their renin/aldosterone status as previously described (Shoback et al., 1983). Subjects were then given a low salt (10 mmol/d) diet for an additional 7 days, and the study protocol was repeated. Blood was also drawn for PRA during low salt intake after 1 h in the upright position. Subjects were classified as normal to high renin if the upright PRA during low salt intake was >2.4 ng of Ang I/ml/h (Shoback et al., 1989). Dietary compliance was assessed by 24-h urine collections at the end of each diet period.

We and others have observed that plasma BK 1–5 concentrations reflect circulating concentrations of exogenous (Murphey et al., 2000a) or endogenous (Sugimoto et al., 1998) bradykinin. To exclude an effect of salt intake on the production or clearance of BK 1–5, we measured the effect of high (200 mmol/d) versus low (10 mmol/d) salt intake on BK 1–5 concentrations achieved during steady-state infusion of bradykinin in three normotensive subjects and on BK 1–5 disappearance rates after the discontinuation of bradykinin. BK 1–5 concentrations were 313 ± 90 and 834 ± 40 fmol/ml during high salt intake and 308 ± 106 and 855 ± 44 fmol/ml during low salt intake during infusion of 25 and 50 ng/kg/min of bradykinin, respectively. The decay constants for the disappearance of BK 1–5 were 0.26 ± 0.12 min⁻¹ and 0.25 ± 0.08 min⁻¹ during high and low salt intake, respectively.

Laboratory Analysis. Blood (5 ml) for BK 1–5 was drawn into a plastic syringe and immediately added to 15 ml of chilled ethanol to denature kallikrein and kininases. After sitting at 4°C for 1 h, samples were centrifuged at 0°C at 2500 rpm for 20 min and stored at −70°C until analysis. Other blood samples were immediately centrifuged, and the plasma was stored at −70°C until analysis. 24-h urine specimens were acidified with 10% (v/v) 1N HCl and stored at 4°C for 1 h. The decay constants for BK 1–5 were 0.26 ± 0.12 min⁻¹ and 0.25 ± 0.08 min⁻¹ during high and low salt intake, respectively.

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Statistical Analysis. Data are presented as mean ± S.E.M. Comparisons of baseline characteristics between the study groups utilized either Chi-square analysis or an unpaired Student's t test. The effect of salt intake on specific endocrine or hemodynamic variables was determined by repeated measures analysis of variance in which the within-subject variables were salt intake and the between-subject variables were hypertension status (normotensive versus hypertensive), ethnicity (white American versus black American), and gender (male versus female). Posthoc comparisons between estimated marginal means were adjusted for multiple comparisons us-
ing the Bonferroni correction. Correlations among variables were made using Pearson coefficients.

**Results**

**Baseline Characteristics.** All subjects tolerated the protocol without serious adverse events. Subject characteristics appear in Table 1. The hypertensive subjects were significantly older and heavier than the normotensive subjects studied. The ethnic and gender distributions of the two groups were statistically similar. Twenty-four-hour urine sodium and potassium excretion was similar in the hypertensive and normotensive groups during both high and low salt intake (Table 1).

**Hemodynamic Response to Dietary Salt Intake.** Mean arterial pressure (MAP) was significantly higher in the hypertensive subjects than the normotensive subjects during both high and low salt intake (Table 2). MAP was significantly greater during high than during low salt intake ($F = 29.6, P < 0.001$). There was a significant interactive effect of salt intake and hypertension status on MAP ($F = 13.4, P = 0.001$), such that the change in MAP from high to low salt intake was greater in the hypertensive subjects than the normotensive subjects ($12.9 \pm 2.6$ versus $-1.7 \pm 1.1$ mm Hg, $P < 0.001$). Indeed, in the normal subjects, there was no significant effect of salt intake on blood pressure. MAP was significantly greater in black Americans than in the white Americans studied within both the normotensive (high salt, 86.6 ± 2.7 versus 79.0 ± 1.7 mm Hg, $P = 0.015$; low salt, 83.0 ± 1.8 versus 78.1 ± 1.5 mm Hg, $P = 0.047$) and hypertensive (high salt, 106.6 ± 3.1 versus 95.3 ± 3.2 mm Hg, $P = 0.02$; low salt, 92.1 ± 4.9 versus 88.4 ± 2.3 mm Hg, $P = N.S.$) groups. There was also a significant interactive effect of salt intake and ethnicity on MAP ($F = 7.6, P = 0.008$), such that the change in MAP from high to low salt was significantly greater in black Americans than in white Americans ($-8.4 \pm 2.0$ versus $-3.3 \pm 1.7$ mm Hg, $P = 0.021$ overall; $-3.6 \pm 1.7$ versus $-0.4 \pm 1.3$ mm Hg in black and white American normotensive subjects, $P = 0.162$; $-15.9 \pm 3.0$ versus $-9.9 \pm 4.2$ mm Hg in black American and white American hypertensive subjects, $P = 0.161$). There was no effect of gender on MAP ($P = 0.968$).

**Endocrine Response to Dietary Salt Intake.** PRA was significantly higher during low than during high salt intake

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Subject characteristics</th>
<th>Normotensive</th>
<th>Hypertensive</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
<td>$n = 35$</td>
<td>$n = 19$</td>
<td></td>
<td></td>
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<tr>
<td>Age (years)</td>
<td>33.1 ± 1.6</td>
<td>43.6 ± 1.9</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Gender (male:female)</td>
<td>15:20</td>
<td>11:8</td>
<td>0.291</td>
<td></td>
</tr>
<tr>
<td>Ethnicity (white:black)</td>
<td>21:14</td>
<td>10:9</td>
<td>0.592</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.7 ± 0.6</td>
<td>30.2 ± 1.5</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Renin status (normal-to-high: low)</td>
<td>30:3</td>
<td>11:7</td>
<td>0.010</td>
<td></td>
</tr>
<tr>
<td>24-h Urinary sodium excretion (mmol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High salt intake</td>
<td>166.1 ± 7.1</td>
<td>163.6 ± 7.9</td>
<td>0.824</td>
<td></td>
</tr>
<tr>
<td>Low salt intake</td>
<td>12.2 ± 2.3</td>
<td>12.1 ± 3.1</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>24-h Urinary potassium excretion (mmol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High salt intake</td>
<td>76.3 ± 3.0</td>
<td>68.7 ± 4.6</td>
<td>0.157</td>
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<tr>
<td>Low salt intake</td>
<td>81.2 ± 4.4</td>
<td>76.7 ± 7.6</td>
<td>0.582</td>
<td></td>
</tr>
</tbody>
</table>

***$P < 0.001$ versus high salt intake.

(F = 44.6, $P < 0.001$; Table 3). PRA was similar in the normotensive and hypertensive groups during each high and low salt intake (Table 3). PRA was significantly higher in the white Americans than in the black Americans studied during both high (1.0 ± 0.2 versus 0.5 ± 0.1 ng of Ang I/ml/H, $P = 0.005$) and low (4.1 ± 0.5 versus 2.5 ± 0.4 ng of Ang I/ml/H, $P = 0.026$) salt intake. There was no effect of gender on PRA ($P = 0.408$). Serum aldosterone was significantly higher during low salt intake than during high salt intake in both normotensive and hypertensive groups ($F = 56.6, P < 0.001$; Table 3). There was an interactive effect of salt intake and hypertension status ($F = 7.2, P = 0.011$), such that the change in plasma aldosterone from high to low salt intake was greater in the normotensive subjects than the hypertensive subjects (372 ± 47 versus 222 ± 44 pmol/liter, $P = 0.025$). There was no significant effect of ethnicity on serum aldosterone concentrations ($P = 0.091$). Serum aldosterone was significantly higher in men than in women during both high (178 ± 17 versus 117 ± 14, $P = 0.007$) and low (558 ± 50 versus 399 ± 47 pmol/liter, $P = 0.024$) salt intake.

There was a significant effect of salt intake on serum ACE activity, such that ACE activity was significantly higher during high than during low salt intake ($F = 16.2, P = 0.001$; Table 3). Although there was no effect of hypertension status alone on ACE activity ($P = 0.281$), there was a significant interactive effect of salt intake and hypertension status on ACE activity ($F = 6.6, P = 0.017$), such that the decrease in ACE activity from high to low salt intake was greater in the hypertensive group than in the normotensive group ($-13.6 ± 3.2$ versus $-3.0 ± 2.2$ U/ml, $P = 0.008$). There was no effect of ethnicity ($P = 0.890$) or gender ($P = 0.398$) on ACE activity.

**Kallikrein-Kinin Response to Dietary Salt Intake.** There was no effect of salt intake ($P = 0.267$) or hypertension status alone ($P = 0.897$) on plasma BK 1–5 concentration.

| TABLE 2 | Hemodynamic response to salt intake |
|---------|-------------------------|-------------------------|-----|
| Characteristic | Normotensive | Hypertensive | $P$ |
| Mean arterial pressure (mm Hg) | $n = 35$ | $n = 19$ | |
| High salt intake | 82.0 ± 1.6 | 100.6 ± 2.5 | <0.001 |
| Low salt intake | 80.1 ± 1.2 | 90.1 ± 2.6 | <0.001 |
| Heart rate (beats/min) | | | |
| High salt intake | 63.1 ± 1.8 | 67.9 ± 1.6 | 0.037 |
| Low salt intake | 64.5 ± 1.9 | 69.4 ± 1.7 | 0.082 |

***$P < 0.001$ versus high salt intake.

*$P < 0.01$ versus high salt intake.
However, there was a significant interactive effect of salt intake and hypertension status on plasma BK 1–5 concentrations ($P = 4.34, P = 0.043$), such that plasma BK 1–5 was significantly lower during low compared with high salt intake in the normotensive group ($P = 0.002$; Fig. 1) but not in the hypertensive group ($P = 0.921$). There was no effect of BMI (all $P > 0.321$), age (all $P > 0.181$), or PRA (all $P > 0.276$) on plasma BK 1–5 concentration during low or high salt intake or in the change in plasma BK 1–5 concentration from high to low salt intake. There was also no effect of ethnicity on plasma BK 1–5 concentration ($P > 0.565$). Within the normotensive group ($r = 0.533, P = 0.004$), but not the hypertensive group ($P = 0.335$), the decrease in plasma BK 1–5 concentration from high to low salt intake correlated with the decrease in MAP from high to low salt intake. The decrease in plasma BK 1–5 with low salt intake varied inversely with the change in aldosterone concentration ($r = -0.443, P = 0.023$) in the normotensive group as well.

There was a significant effect of salt intake ($F = 43.4, P < 0.001$), but not hypertension status ($P = 0.657$), on urinary kallikrein excretion. Thus, urinary kallikrein excretion was significantly higher during low than during high salt intake in both normotensive and hypertensive subjects (Fig. 2). The increase in urinary kallikrein excretion from high to low salt intake correlated with the increase in serum aldosterone concentration ($r = 0.341, P = 0.031$).

There was a significant effect of ethnicity ($F = 7.6, P = 0.010$) and a significant interactive effect of salt intake and ethnicity ($F = 6.0, P = 0.020$) on urinary kallikrein excretion. Urinary kallikrein excretion was significantly lower in black Americans compared with white Americans during both low and high salt intake in the normotensive but not the hypertensive group (Fig. 3). There was also a significant effect of gender ($F = 5.7, P = 0.023$) on urinary kallikrein excretion, with urinary kallikrein excretion being higher in the women studied than in the men. When urinary kallikrein excretion was analyzed separately in the men and women studied, there was a significant effect of salt intake on urinary kallikrein excretion in both gender groups (Fig. 3). There tended to be an interactive effect of salt intake and hypertension status ($F = 4.2, P = 0.057$) in the men studied, but not in the women ($P = 0.493$). There was no significant effect of salt intake ($P = 0.354$), hypertension status ($P = 0.078$), ethnicity ($P = 0.737$), or gender ($P = 0.819$) on urinary BK 1–5 excretion (Fig. 2).

**Fig. 1.** Effect of high (black bars) and low (hatched bars) salt intake on plasma BK 1–5 concentration in normotensive and hypertensive subjects. *, $P < 0.005$ versus high salt intake.

Discussion

In the vasculature, circulating bradykinin causes vasodilation by stimulating the synthesis of nitric oxide, prostacyclin, and the endothelium-derived hyperpolarizing factor (Vanhoutte, 1989). In the kidney, local activity of the kallikrein-kinin system influences regional blood flow and sodium excretion (Levy et al., 1977; Carretero and Scicl, 1980). Numerous studies in humans indicate that urinary (renal) kallikrein excretion is increased during low compared with high salt intake (Margolius et al., 1974; Levy et al., 1977; O’Connor, 1982; Hughes et al., 1988; Hilgenfeldt et al., 1998). In contrast, Hilgenfeldt et al. (1998) reported that, whereas urinary kallikrein excretion is increased during low salt intake in normal volunteers, circulating plasma kallikrein and bradykinin concentrations are increased during high salt intake. The present study confirms this differential effect of salt intake on the circulating and renal kallikrein-kinin systems and indicates that the increase in circulating bradykinin (as measured by its stable metabolite BK 1–5) in response to high salt intake is impaired in subjects with hypertension.

As observed in previous studies, urinary kallikrein excretion was significantly greater during low than during high salt intake (Margolius et al., 1974; Levy et al., 1977; O’Connor, 1982; Hughes et al., 1988; Hilgenfeldt et al., 1998). This effect of salt intake on urinary kallikrein excretion was observed in white and black Americans and men and women alike. However, as observed in previous studies, urinary kallikrein excretion was significantly lower in black Americans studied compared with white Americans (Levy et al., 1977; Hughes et al., 1988; Song et al., 2000) and significantly higher in the women studied compared with the men (Hughes et al., 1988; Albano et al., 1994; Song et al., 2000). Numerous previous studies, conducted in predominantly male populations, indicate that urinary kallikrein excretion is decreased in subjects with salt-sensitive or low renin hypertension, although not necessarily in subjects with normal
There was no effect of salt intake on urinary BK-1 bradykinin (Carretero and Scicli, 1980). In the present study, kallidin is degraded by urinary aminopeptidases to form al., 2000a). While urinary (tissue) kallikrein forms kallidin, the normotensive males studied, as previously reported significantly decreased in the hypertensive as compared with the normotensive males studied, as previously reported (Margolius et al., 1971, 1974).

We and others have reported previously that urinary bradykinin or BK1–5 concentrations reflect the renal production of bradykinin (Carretero and Scicli, 1980; Murphey et al., 2000a). While urinary (tissue) kallikrein forms kallidin, kallidin is degraded by urinary aminopeptidases to form bradykinin (Carretero and Scicli, 1980). In the present study, there was no effect of salt intake on urinary BK1–5 excretion, even though urinary kallikrein excretion was increased during low salt intake. This concurs with data from Hilgenfeldt et al. (1998) who reported no effect of salt intake on urinary kallidin or bradykinin excretion despite increased renal kallikrein excretion during low salt intake. The authors attributed this to an opposing down-regulation of renal synthesis of low molecular weight kininogen during low salt intake. Because we did not measure urinary kininogen or kallidin excretion in the present study, we cannot address this possibility.

Serum ACE activity was significantly increased during high compared with low salt intake. This differs from the data of Hilgenfeldt et al. who reported an opposite effect of salt intake on serum ACE activity in normal human subjects. Studies in animal models provide conflicting data as to the effect of salt intake on ACE. For example, some studies in normotensive mice (Tamura et al., 1998), Wistar-Kyoto rats (Kreutz et al., 1995), and rodent models of hypertension (Michel et al., 1994; Zhao et al., 2000) have indicated that tissue ACE expression is increased with high salt intake. In contrast, other studies in rats (Fox et al., 1992; Michel et al., 1994) indicate that tissue ACE expression is unchanged or decreased during high salt intake. The mechanism through which salt intake modulated serum ACE activity in the present study is not known, but it could involve effects of sodium on tissue ACE expression, cleavage and secretion of ACE, or ACE enzyme activity. Data from animal studies indicate that Ang II regulates tissue ACE expression through an ANG2 receptor-mediated pathway (Hunley et al., 2000), supporting the hypothesis that increased Ang II concentrations could decrease tissue ACE expression during low salt intake in humans.

Because circulating BK1–5 concentrations reflect not only the production of bradykinin but also the degradation of bradykinin by ACE, changes in ACE activity could have confounded the interpretation of the effect of salt intake on systemic bradykinin in the present study. However, ACE activity did not change significantly with salt intake in the normotensive subjects, indicating that the increase in circulating BK1–5 observed with high salt intake reflected increased bradykinin synthesis rather than increased degradation of bradykinin to BK1–5. Moreover, the significantly greater ACE activity during high compared with low salt intake observed in the hypertensive subjects would have increased the degradation of bradykinin to BK1–5 and, therefore, cannot account for the lack of effect of salt intake on BK1–5 observed in hypertension.

The hypertensive group in the current study was significantly older and heavier and tended to have a greater number of low renin subjects as compared with the normotensive group. These differences may also have confounded the interpretation of the effect of salt on plasma BK1–5. However, when these variables were entered into the analysis, there was no effect of age, BMI, or PRA on BK1–5 concentrations, indicating that it is unlikely that differences in age and BMI or renin status between the groups can explain the observed loss of sodium modulation of plasma BK1–5 in the hypertensive group.

Although this study and the investigation of Hilgenfeldt et al. have demonstrated that low salt intake increases urinary kallikrein excretion but decreases plasma bradykinin concentration, the mechanism for the differential effect of salt intake on the systemic and renal kallikrein-kinin systems is not known. Studies in animal models and in humans indicate
that aldosterone stimulates renal synthesis and urinary excretion of kallikrein (Margolius et al., 1974; Fejes-Toth and Naray-Fejes-Toth, 1984; Kaufman et al., 1986; Albano et al., 1994). In this study, as in previous studies, urinary kallikrein excretion during low salt intake correlated with serum aldosterone concentrations. In contrast, plasma BK 1 increase during high salt intake correlated with systemic bradykinin levels. Where volume is decreased (e.g., low salt intake), high salt intake increases systemic bradykinin levels. Where volume is increased (e.g., high salt intake), high salt diet decreases systemic bradykinin levels. Where volume is increased (e.g., low salt intake), high salt intake decreases systemic bradykinin levels. Where volume is decreased (e.g., low salt intake), high salt intake decreases systemic bradykinin levels.

In this study, as in previous studies, urinary kallikrein excretion in the present study provides evidence that the increase in BK excretion during low salt intake correlated with systemic bradykinin levels. Where volume is decreased (e.g., low salt intake), high salt intake increases systemic bradykinin levels. Where volume is increased (e.g., high salt intake), high salt diet decreases systemic bradykinin levels. Where volume is decreased (e.g., low salt intake), high salt intake decreases systemic bradykinin levels. Where volume is increased (e.g., high salt intake), high salt diet decreases systemic bradykinin levels.

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In this study, as in previous studies, urinary kallikrein excretion in the present study provides evidence that the increase in BK excretion during low salt intake correlated with systemic bradykinin levels. Where volume is decreased (e.g., low salt intake), high salt intake increases systemic bradykinin levels. Where volume is increased (e.g., high salt intake), high salt diet decreases systemic bradykinin levels. Where volume is decreased (e.g., low salt intake), high salt intake decreases systemic bradykinin levels. Where volume is increased (e.g., high salt intake), high salt diet decreases systemic bradykinin levels.

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