Loss of Sodium Modulation of Plasma Kinins in Human Hypertension

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Abbreviations: ACE, angiotensin-converting enzyme; PRA, plasma renin activity; KKS, kallikrein-kinin system; ANOVA, analysis of variance; MAP, mean arterial pressure

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Abstract

We studied the effect of salt intake and hypertension on the systemic kallikrein-kinin system (KKS), as measured by 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 in balance on a high- (200 mmol/d) or low- (10 mmol/d) salt diet. Salt restriction decreased mean arterial pressure (MAP, P<0.001 overall) and 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 to 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, change in plasma BK 1-5 from high- to low-salt intake correlated with change in MAP (r=0.533, P=0.004). Urinary kallikrein was higher during low- compared to 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, while under basal conditions endogenous bradykinin does not play an important role in regulating blood pressure, 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).

Characterization of 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. While 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, delineation of the role of bradykinin in sodium homoeostasis and blood pressure regulation in humans has been further complicated by technical difficulties in accurately measuring plasma bradykinin. While 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 kallikrien-kinin systems. Both theoretically could be involved in blood pressure regulation but potentially via 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 individuals with essential hypertension compared to normotensive individuals (Margolius et al., 1971; Levy et al., 1977) and in black Americans compared to white Americans (Levy et al., 1977). However, 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) have reported that, whereas urinary kallikrein excretion is increased, plasma kallikrein and bradykinin are decreased during salt restriction compared to salt repletion in healthy volunteers. The investigators did not report the effect of salt intake on plasma bradykinin concentrations in hypertensive individuals and the bradykinin concentrations were higher than those reported by other groups (Nussberger et al., 1998; Duncan et al., 2000). In contrast, Wang 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 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 therefore to characterize the effect of salt intake on plasma concentrations of the stable bradykinin metabolite, BK 1-5, in normotensive and hypertensive individuals and contrast changes in its levels with changes in activity of the renin-angiotensin-aldosterone system and urinary kallikrein.
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 mmHg and as hypertensive if they had a seated blood pressure >145/95 mmHg on three occasions. Except for hypertension, all subjects were healthy. Individuals with secondary forms of hypertension were excluded. All anti-hypertensive medications were discontinued for three weeks prior to the study and subjects were taking no medications during the study.

General Protocol. Subjects were participating 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 providing a daily intake of 200 mmol sodium (high salt), 100 mmol potassium, 800 mg calcium, and 200 to 300 g carbohydrate for 7 days. Beginning on the 7th day subjects were asked to collect all of their urine for 24 hours 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 one hour 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 described (Shoback et al., 1983). Subjects were then provided 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 following one hour in the upright position. Subjects were classified as normal-to-high renin if the upright PRA during low-salt intake was $\geq 2.4$ ng Ang I/ml/hr (Shoback et al., 1983). Dietary compliance was assessed by 24-hour urine collection 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. In order 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 3 normotensive subjects, as well as on BK 1-5 disappearance rates following discontinuation of bradykinin. BK 1-5 concentrations were $313 \pm 90$ and $834 \pm 40$ fmol/ml during high salt intake and $308 \pm 106$ and $858 \pm 44$ fmol/ml during low salt intake during infusion of 25 and 50 ng/kg/min of bradykinin, respectively. The decay constants for disappearance of BK 1-5 were $0.26 \pm 0.12$ min$^{-1}$ and $0.25 \pm 0.08$ min$^{-1}$, during high and low salt, respectively.

**Laboratory Analysis.** Blood (5 ml) for BK 1-5 was drawn into a plastic syringe and immediately added to 15 ml chilled ethanol to denature kallikrein and kininases. After sitting at 4°C for 1 hr, samples were centrifuged at 0°C at 2500 RPM for 20 minutes and stored at −70°C until analysis. Other blood samples were immediately centrifuged and the plasma stored at −70°C until analysis. 24-hour urine specimens were acidified with 10% (v/v) 1N HCl and stored at −70°C for BK 1-5 analysis. Urinary BK 1-5 concentrations are stable in acidified urine for up to 18 months under these conditions (unpublished data). BK 1-5 in blood and urine was determined by liquid chromatography mass spectrometry (Murphey et al., 2001). The within-subject and between-subject variability of BK 1-5 are 9.6% and 37.8%, respectively, with this assay.
Urinary kallikrein activity was determined as described (Wang et al., 1995). PRA was determined by radioimmunoassay of angiotensin I generated at 37°C, pH 6.0 (INCSTAR Corp., Stillwater, MN). Serum aldosterone levels were determined by radioimmunoassay (Diagnostic Products Corp., Los Angeles, CA). Plasma ACE activity was determined by a spectrophotometric method (Sigma, St. Louis, MO). Urinary sodium and potassium were measured by flame photometry using lithium as the internal standard (Autoanalyzer, Technicon, Buffalo Grove, IL).

Statistical Analysis. Data are presented as mean ± standard error of the mean (SEM). 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 ANOVA 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). Post hoc comparisons between estimated marginal means were adjusted for multiple comparisons using 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 were similar in the hypertensive and normotensive groups during both high salt 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 salt intake 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 salt to low salt intake was greater in the hypertensive subjects than the normotensive subjects (−12.9 ± 2.6 versus −1.7 ± 1.1 mmHg, P<0.001). Indeed in the normal subjects, there was no significant effect of salt intake on blood pressure. MAP was significantly greater in the black Americans than in the white Americans studied within both the normotensive (high salt 86.6±2.7 versus 79.0±1.7 mmHg, P=0.015; low salt 83.0±1.8 versus 78.1±1.5 mmHg, P=0.047) and hypertensive (high salt 106.6±3.1 versus 95.3±3.2 mmHg, P=0.02; low salt 92.1±4.9 versus 88.4±2.3 mmHg, P=NS) groups. There was also a significant interactive effect of salt intake and ethnicity on MAP (F=7.6, P=0.008) such that change in MAP from high salt to low salt was significantly greater in black Americans than in white Americans (−8.4±2.0 versus −3.3±1.7 mmHg, P=0.021 overall; −3.6±1.7 versus −0.4±1.3 mmHg in black and white normotensive subjects, P=0.162; −
15.9±3.0 versus −9.9±4.2 mmHg in black and white 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 salt intake than during 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 Ang I/ml/hr, P=0.005) and low (4.1±0.5 versus 2.5±0.4 ng Ang I/ml/hr, 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 salt to low salt intake was greater in the normotensive subjects than the hypertensive subjects (372±47 vs. 222±44 pmol/L, 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 salt (178±17 versus 117±14, P=0.007) and low salt (558±50 versus 399±47 pmol/L, P=0.024) intake.

There was a significant effect of salt intake on serum ACE activity such that ACE activity was significantly higher during high salt intake 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 salt to low salt intake was greater in the hypertensive group than in the normotensive group (-13.6±3.2 versus -
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. However, there was a significant interactive effect of salt intake and hypertension status on plasma BK 1-5 concentrations (F=4.34, P=0.043), such that plasma BK 1-5 was significantly lower during low salt intake compared to high salt intake in the normotensive group (P=0.002, Figure 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 salt or high salt intake or in the change in plasma BK 1-5 concentration from high salt to low salt intake. There was 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 salt to low salt intake correlated with the decrease in MAP from high salt 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 salt intake than during high salt intake in both normotensive and hypertensive subjects (Figure 2). The increase in urinary kallikrein excretion from high salt 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) as well as 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 to white Americans during both low salt and high salt intake in the normotensive but not the hypertensive group (Figure 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 studied. 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 (Figure 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 (Figure 2).
Discussion

In the vasculature, circulating bradykinin causes vasodilation by stimulating the synthesis of nitric oxide, prostacyclin and 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 Scicli, 1980). Numerous studies in humans indicate that urinary (renal) kallikrein excretion is increased during low salt intake compared to during 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) have 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 individuals with hypertension.

As observed in previous studies, urinary kallikrein excretion was significantly greater during low salt intake 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. Also as observed in previous studies, however, urinary kallikrein excretion was significantly lower in the black Americans studied compared to the white Americans studied (Levy et al., 1977; Hughes et al., 1988; Song et al., 2000) and significantly higher in the women studied compared to the men studied (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 individuals with salt-sensitive or low renin hypertension, although not necessarily in individuals with normal-to-high renin hypertension (Mersey et al., 1979; Hughes et al., 1988; Ferri et al., 1994). In the present study of predominantly normal-to-high renin hypertensive individuals of both genders, there was no effect of hypertension on urinary kallikrein excretion among the overall population. On the other hand, urinary kallikrein excretion during low salt intake was significantly decreased in the hypertensive as compared to normotensive males studied, as previously reported (Margolius et al., 1971; 1974).

We and others have reported previously that urinary bradykinin or BK 1-5 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 BK 1-5 excretion even though urinary kallikrein excretion was increased during low salt intake. This concurs with data from Hilgenfeldt 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 salt intake compared to during low salt intake. This contrasts to 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. The mechanism through which salt intake modulated serum ACE activity in the present study is not known but could involve effects of sodium on tissue ACE expression, on the cleavage and secretion of ACE, or on ACE enzyme activity. Data from animals studies indicating that Ang II regulates tissue ACE expression through an AT2 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 BK 1-5 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 BK 1-5 observed with high salt intake reflected increased bradykinin synthesis rather than increased degradation of bradykinin to BK 1-5. Moreover, the significantly greater ACE activity during high salt compared to low salt intake observed in the hypertensive subjects would have increased the degradation of bradykinin to BK 1-5 and, therefore, cannot account for the lack of effect of salt intake on BK 1-5 observed in hypertension.

The hypertensive group in the current study was significant older and heavier and tended to have a greater number of low-renin individuals as compared to the normotensive group. These differences may also have confounded the interpretation of the effect of salt on plasma BK 1-5. However, when these variables were entered into the analysis, there was no effect of age,
BMI or PRA on BK 1-5 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 BK 1-5 in the hypertensive group.

While 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 1-5 concentrations correlated inversely with circulating aldosterone concentrations. On the other hand, the increase in BK 1-5 concentration during high salt intake correlated directly with the increase in MAP, suggesting a mechanism whereby increased blood pressure stimulates the synthesis of the vasodilator bradykinin. Further studies are needed to address the mechanism for this effect of salt intake on bradykinin synthesis. However, the current study in concert with previous data does offer a possible hypothesis for the relationship between salt intake and the role of the kallikrein-kinin systems in blood pressure regulation. The systemic system is primarily involved in regulating vascular tone. Thus, under conditions where volume is increased (e.g., high salt intake), increased systemic bradykinin levels increase vascular capacity. Where volume is decreased (e.g., low salt intake), bradykinin levels are decreased. In contrast, the renal kallikrein-kinin system responds not to systemic vascular tone but to local changes in blood flow. Thus, when the RAAS is activated by a low salt diet, urinary kallikrein is increased to counteract the local, renal vasoconstrictive effects of
Ang II and vice versa with high salt diet and suppression of the RAAS. It appears that in, at least, some hypertensive subjects, this give-and-take relationship has been disturbed thereby contributing to the increased blood pressure.

In conclusion, the kallikrein-kinin systems cause vasodilation and affect local renal blood flow and sodium handling (Bhoola et al., 1992). Previous investigations in humans have demonstrated that, while urinary (renal) kallikrein excretion is increased during low salt intake, plasma (systemic) bradykinin concentrations increase during high salt intake (Margolius et al., 1974; Levy et al., 1977; Hilgenfeldt et al., 1998). This increase in plasma bradykinin concentration with high salt intake may be expected to modulate the hypertensive effects of sodium retention by causing increased vasodilation (Vanhoutte, 1989). Data from animal models support the hypothesis that the kallikrein-kinin system modulates the effect of high salt intake on blood pressure (Madeddu et al., 1993; 1998; Cervenka et al., 1999). In humans, the present study provides evidence that the increase in circulating kinins in response to high salt intake is impaired in individuals with essential hypertension.
References


Footnotes

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Figure Legends

Figure 1. Effect of high salt (black bars) and low salt (hatched bars) intake on plasma BK 1-5 concentration in normotensive and hypertensive individuals. *P<0.005 versus high salt.

Figure 2. Effect of high salt (black bars) and low salt (hatched bars) intake on (A) urinary BK 1-5 and (B) urinary kallikrein excretion in normotensive and hypertensive individuals. *P<0.01, **P<0.001 versus high salt intake.

Figure 3. Effect of salt intake and hypertension status on urinary kallikrein excretion in (A) white Americans, (B) black Americans, (c) men, and (D) women. *P<0.05, **P<0.01, ***P<0.001 versus high salt intake; †P<0.05, ††P<0.01 versus white Americans; ‡P<0.05 versus normotensive; §P<0.01 versus men.
Table 1. Subject characteristics.

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<td>11: 7</td>
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24-hour urinary sodium excretion (mmol)

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<tr>
<td>High salt intake</td>
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24-hour urinary potassium excretion (mmol)

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Mean ± standard error of the mean or N.  ***P<0.001 versus high salt intake.
Table 2. Hemodynamic response to salt intake

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<td>(N = 19)</td>
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<td>High salt intake</td>
<td>82.0 ± 1.6</td>
<td>100.6 ± 2.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low salt intake</td>
<td>80.1 ± 1.2</td>
<td>90.1 ± 2.6***</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart Rate (beats/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High salt intake</td>
<td>63.1 ± 1.8</td>
<td>67.9 ± 1.6</td>
<td>0.037</td>
</tr>
<tr>
<td>Low salt intake</td>
<td>64.5 ± 1.9</td>
<td>69.4 ± 1.7</td>
<td>0.082</td>
</tr>
</tbody>
</table>

Mean ± standard error of the mean. ***P<0.001 versus high salt intake.
Table 3. Endocrine response to salt intake

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normotensive (N = 30)</th>
<th>Hypertensive (N = 17)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Renin Activity (ng/mL/hr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High salt intake</td>
<td>0.71 ± 0.08</td>
<td>0.96 ± 0.30</td>
<td>0.296</td>
</tr>
<tr>
<td>Low salt intake</td>
<td>3.62 ± 0.37**</td>
<td>3.14 ± 0.79**</td>
<td>0.536</td>
</tr>
<tr>
<td>Aldosterone (pmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High salt intake</td>
<td>133 ± 14</td>
<td>169 ± 22</td>
<td>0.138</td>
</tr>
<tr>
<td>Low salt intake</td>
<td>530 ± 47**</td>
<td>391 ± 47**</td>
<td>0.063</td>
</tr>
<tr>
<td>Serum ACE Activity (U/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High salt intake</td>
<td>37.1 ± 3.1</td>
<td>47.8 ± 4.9</td>
<td>0.059</td>
</tr>
<tr>
<td>Low salt intake</td>
<td>33.7 ± 2.6</td>
<td>34.2 ± 3.7**</td>
<td>0.899</td>
</tr>
</tbody>
</table>

Mean ± standard error of the mean. **P<0.01 versus high salt intake.
Figure 1

The bar graph shows the plasma BK 1-5 levels (fmol/ml) in normotensive and hypertensive individuals under high salt and low salt conditions. The graph indicates a statistically significant difference (*) between the groups. High salt conditions show higher levels of BK 1-5 in normotensive individuals compared to hypertensive individuals. Low salt conditions show similar levels across both groups.