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## Diet-sensitive prognostic markers for cardiovascular and renal disease

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## Chapter 2

# Effects of Potassium Supplementation on Markers of Osmoregulation and Volume Regulation: Results of a Fully Controlled Dietary Intervention Study

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## Abstract

**Objective.** Lifestyle measures including dietary sodium restriction and increased potassium intake are recognized to lower blood pressure. Potassium was found to be effective in reducing blood pressure at higher levels of sodium intake, but to have little effect when sodium intake is restricted. The humoral mechanisms underlying these sodium intake dependent effects of potassium are unknown. We investigated the effects of potassium supplementation on top of a fully controlled sodium-restricted diet on markers of osmoregulation and volume regulation.

**Methods.** In this post-hoc analysis, we included 35 (pre)hypertensive subjects participating in a randomized, double-blind, placebo-controlled crossover trial. Subjects received capsules containing sodium (3.0 g [130 mmol]/day), potassium (2.8 g [72 mmol]/day), or placebo for three four-week periods. Linear mixed-effect models were used to estimate the effects of potassium supplementation compared to placebo. Skewed data were ln-transformed before analysis.

**Results.** Increased potassium intake was associated with a significant decrease in 24-h blood pressure (-3.6/-1.6 mmHg). Furthermore, we found a significant decrease in ln MR-proANP (-0.08 [95% CI: -0.15, -0.01] pmol/L, P=0.03) and significant increases in heart rate (2.5 [0.9, 4.0] bpm, P=0.002), ln plasma copeptin (0.11 [0.01, 0.20] pmol/L, P=0.02), ln renin (0.34 [0.08, 0.60]  $\mu$ U/mL, P=0.01), and ln aldosterone (0.14 [0.07, 0.22] nmol/L, P<0.001) compared with placebo.

**Conclusions.** We found that potassium has blood pressure-lowering effects during sodium restriction. These blood pressure-lowering effects, however, seem mitigated by several counter regulatory mechanisms (i.e., increased secretion of vasopressin, stimulation of RAAS, and increased heart rate) that were activated to maintain volume homeostasis and counterbalance the decrease in blood pressure.

## Introduction

Given the high prevalence of hypertension and the concomitant increased risks for cardiovascular and renal disease (1,2), hypertension is an important worldwide public-health challenge (3). Lifestyle measures including dietary sodium restriction and increased potassium intake are recognized to lower blood pressure and cardiovascular risk (4-6).

A key aspect in long-term regulation of blood pressure is fluid balance, which is precisely regulated by means of osmoregulation and volume regulation. Any increase in plasma osmolarity, which is mainly determined by the plasma sodium concentration, is normally counterbalanced by an increase in vasopressin to maintain osmotic homeostasis (7). Multiple effectors are involved in volume regulation including the renin-angiotensin aldosterone system (RAAS) that stimulates sodium reabsorption (8), natriuretic peptides that promote sodium excretion (9), and vasopressin that stimulates water reabsorption in the kidneys (7,10).

Previous studies, including meta-analyses of randomized controlled trials, have suggested that the blood pressure-lowering effects of potassium are more pronounced at higher levels of sodium intake (6,11,12). During sodium restriction, potassium intake was found to have little or no effect on blood pressure (13). To date, it is not known whether a modest blood pressure-lowering effect of potassium supplementation during sodium restriction is biologically plausible. Also, the humoral mechanisms involved in the blood pressure-lowering effects of potassium supplementation have poorly been described. Therefore, our aim was to investigate whether there could be biological plausibility for a modest blood pressure-lowering effect of potassium supplementation during sodium restriction. To this end, we investigated the humoral effects of potassium supplementation during a fully controlled sodium-restricted diet using a panel of markers that are involved in osmoregulation and volume regulation. We additionally investigated the effects of sodium supplementation, with surmised opposite changes in markers of osmoregulation and volume regulation.

## Materials and Methods

### *Study Protocol and Subjects*

The current study is a post-hoc analysis of a randomized, double-blind, placebo-controlled crossover trial in which subjects were on a fully controlled diet for a period of 13 weeks, as described previously (14). The study was designed to examine the

effects of sodium and potassium supplementation on blood pressure and vascular function in untreated (pre)hypertensive individuals (i.e., subjects with a fasting office systolic blood pressure between 130 and 159 mmHg) (14). In brief, at the end of a one-week run-in period ('baseline'), subjects were randomized to take 8 sodium chloride capsules (i.e., 3.0 g [130 mmol] sodium), 8 potassium chloride capsules (i.e., 2.8 g [72 mmol] potassium) or 8 placebo capsules (cellulose) daily, for four weeks each, while they were provided with the fully controlled diet. The fully controlled diet provided on average 2.4 g (104 mmol) of sodium, based on the recommended maximum sodium intake of 2.0-2.4 g per day (which equals 87-104 mmol sodium or 5-6 g salt per day) (15,16), and 2.3 g (59 mmol) of potassium per day for a 2500-kcal intake. Subjects were weighed twice a week and if needed, their energy intake was adjusted to keep body weight constant.

Nonsmoking men and women aged 40 to 80 years, who had a fasting office systolic blood pressure between 130 and 159 mmHg were eligible for the study. Exclusion criteria were a history of diabetes mellitus, cardiovascular, gastrointestinal, liver, or renal diseases; BMI >40 kg/m<sup>2</sup>; use of medication known to affect the cardiovascular system; use of nutritional supplements; an energy-restricted or medically prescribed diet; unstable body weight in the preceding two months; alcohol use over 21 (women) or 28 (men) consumptions per week; and pregnant or lactating women. Of the 37 Caucasian subjects that were included and randomized in the study, 36 completed the study. One subject withdrew because of experiencing gastrointestinal complaints. Given the effects of trauma or severe infection on plasma copeptin (17), one subject was excluded from all analyses because of severe trauma during the placebo study period and one subject was excluded only from analyses on the effects of potassium because of severe infection during the potassium intervention period. Written consent was obtained from all subjects. The study was approved by the Medical Ethics Committee of Wageningen University and was in adherence to the Declaration of Helsinki. The trial was registered at ClinicalTrials.gov (registration no. NCT01575041).

### *Measurements*

At baseline and at the end of each four-week intervention, subjects collected a 24-h urine sample and underwent 24-h ambulatory blood pressure and heart rate monitoring (Spacelabs 90127 devices, Spacelabs Medical Inc. Redmond, WA, USA). At the research center, in a fasting state, anthropometrics and blood pressure were measured, and blood was sampled. Subjects rested at least 10 minutes before office brachial blood pressure was assessed in the supine position with an automated oscillometric device (Dinamap Pro 100, KP Medical, Houten, the Netherlands).

Serum and urinary sodium and potassium concentrations were measured using the ion-selective electrodes module on the Roche Modular P (Roche Diagnostics, Mannheim, Germany); plasma copeptin and MR-proANP using an automated sandwich immunoassay (KRYPTOR, BRAHMS GmbH, Hennigsdorf/Berlin, Germany); plasma NT-proBNP using the Roche Modular E170 (Roche Diagnostics, Mannheim, Germany); and plasma renin and aldosterone concentrations using an automated sandwich immunochemiluminescent assay (LIAISON®, Diasorin, DiaSorin Ltd, Schiphol Rijk, The Netherlands). Other serum and urinary parameters were assessed using standard laboratory methods. Serum osmolality was calculated using the equation  $1.9 * ([Na] + [K]) + [glucose] + 0.5 * [urea] + 5$  (18). The creatinine-based Chronic kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to estimate glomerular filtration rate (eGFR) (19).

### *Statistical Analysis*

Analyses were performed using SAS 9.2 software (SAS Institute, Cary, North Carolina, USA) and SPSS version 22.0 for Windows (IBM Corporation, Chicago, Illinois, USA). Data are reported as mean with standard deviation for variables with a normal distribution or geometric mean with 95% CI for variables with a skewed distribution. Nominal data are presented as the number of subjects with percentage (n [%]). A two-sided P-value <0.05 was considered to indicate statistical significance.

To estimate the effects of potassium and sodium supplementation compared to placebo on clinical parameters, we used linear mixed-effect models for repeated measurements, using the compound symmetry covariance structure with 'treatment' and 'period' as fixed effects and 'subject' as random effect. Skewed data were logarithmically transformed before statistical analysis.

## **Results**

### *Baseline Characteristics*

During screening, mean 24-h urinary sodium excretion was 152 mmol (i.e., 3.5 g sodium or 8.7 g of salt), which reduced to 91 mmol after one-week run-in (i.e., baseline). Mean 24-h potassium excretion during screening was 82 mmol (i.e., 3.2 g potassium), which reduced to 49 mmol after run-in. Average office blood pressure was 146/81 mmHg during screening and 134/76 mmHg after the one-week run-in period on controlled diet. Baseline characteristics of the study subjects are shown in Table 1.

**Table 1.** Baseline characteristics of the study subjects (n=35).

	All subjects <sup>a</sup>
<b>Demographics</b>	
Male sex (n, %)	23 (66)
Age (years)	66 ± 9
<b>Clinical measurements</b>	
BMI (kg/m <sup>2</sup> )	27.4 ± 4.7
Body weight (kg)	84.9 ± 18.5
SBP (mmHg)	134 ± 15
DBP (mmHg)	76 ± 8
Heart rate (bpm)	61 ± 6
<b>Fasting serum/plasma parameters</b>	
Sodium (mmol/L)	143 ± 2
Potassium (mmol/L)	4.3 ± 0.3
Serum osmolarity (mmol/L)	294 ± 3
Total cholesterol to HDL ratio	3.9 ± 1.0
<b>Renal function parameters</b>	
Serum urea (mmol/L)	5.4 ± 1.0
Serum creatinine (μmol/L)	81 ± 13
eGFR (mL/min/1.73m <sup>2</sup> )	79 ± 12
ACR (mg/mmol)	0.41 (0.28-0.59)
<b>Urinary parameters</b>	
Sodium excretion (mmol/24 h) <sup>b</sup>	91 ± 27
Potassium excretion (mmol/24 h) <sup>c</sup>	49 ± 14

Abbreviations: ACR, urinary albumin to creatinine ratio; eGFR, estimated glomerular filtration rate.

<sup>a</sup> Data are presented as mean ± SD, geometric mean (95% CI), or n (%).

<sup>b</sup> To convert sodium in mmol/24 h to mg/24 h multiply by 23.

<sup>c</sup> To convert potassium in mmol/24 h to mg/24 h multiply by 39.

*Effects of Potassium and Sodium Supplementation*

The effects of potassium and sodium supplementation on clinical parameters are shown in Table 2. After four weeks of potassium supplementation, 24-h blood pressure and plasma MR-proANP decreased significantly, whereas plasma copeptin, renin, aldosterone, serum urea, and 24-h heart rate increased significantly compared with placebo (Table 2). After four weeks of sodium supplementation, we found significant increases in 24-h blood pressure and plasma concentrations of copeptin and natriuretic peptides (i.e., NT-proBNP and MR-proANP), whereas plasma renin and aldosterone concentrations decreased significantly compared with placebo (Table 2).



Table 2. Effects of potassium and sodium supplementation in 35 untreated (pre)hypertensive adults.

	Values after four weeks of intervention <sup>a</sup>			Treatment effect <sup>b</sup>			
	Potassium <sup>c</sup>	Sodium	Placebo	Potassium vs. Placebo <sup>c</sup>	P	Sodium vs. Placebo	P
<b>Urinary parameters</b>							
Sodium (mmol/24 h) <sup>d</sup>	95 ± 39	201 ± 55	102 ± 36	-7 (-23, 10)	0.4	99 (83, 115)	<0.001
Potassium (mmol/24 h) <sup>e</sup>	116 ± 32	53 ± 16	54 ± 16	62 (54, 70)	<0.001	-2 (-10, 6)	0.6
Volume (mL/24 h)	1745 ± 775	1928 ± 838	1900 ± 803	-133 (-370, 104)	0.3	20 (-214, 255)	0.9
<b>Clinical measurements</b>							
24-h SBP (mmHg)	125.9 ± 13.6	137.2 ± 14.4	129.3 ± 14.3	-3.6 (-6.7, -0.6)	0.02	8.0 (5.0, 11.1)	<0.001
24-h DBP (mmHg)	75.1 ± 8.0	79.3 ± 9.0	76.5 ± 8.4	-1.6 (-3.2, -0.04)	0.04	2.9 (1.3, 4.5)	<0.001
24-h heart rate (bpm)	69.2 ± 8.2	65.4 ± 9.3	66.3 ± 9.1	2.5 (0.9, 4.0)	0.002	-0.8 (-2.4, 0.7)	0.3
<b>Serum/plasma parameters</b>							
Sodium (mmol/L)	142.7 ± 1.5	143.8 ± 1.5	143.4 ± 1.2	-0.7 (-1.2, -0.2)	0.003	0.4 (-0.1, 0.9)	0.09
Potassium (mmol/L)	4.41 ± 0.31	4.17 ± 0.34	4.28 ± 0.32	0.13 (0.05, 0.21)	0.003	-0.10 (-0.19, -0.02)	0.01
Serum osmolarity (mmol/L)	293 ± 3	294 ± 3	294 ± 2	-1 (-2, 0)	0.04	0 (0, 1)	0.3
Copeptin (pmol/L)	7.2 (5.9-8.9)	7.6 (6.3-9.2)	6.4 (5.4-7.6)				
Ln Copeptin (pmol/L)	1.98 ± 0.60	2.03 ± 0.55	1.86 ± 0.51	0.11 (0.01, 0.20)	0.02	0.18 (0.08, 0.27)	<0.001
NT-proBNP (ng/L)	68 (48-96)	102 (72-144)	73 (51-105)				
Ln NT-proBNP (ng/L)	4.22 ± 0.98	4.62 ± 1.00	4.29 ± 1.06	-0.08 (-0.24, 0.08)	0.3	0.33 (0.17, 0.49)	<0.001
MR-proANP (pmol/L)	83 (73-94)	100 (86-116)	89 (77-103)				
Ln MR-proANP (pmol/L)	4.42 ± 0.37	4.60 ± 0.43	4.49 ± 0.41	-0.08 (-0.15, -0.01)	0.03	0.11 (0.04, 0.18)	0.002

Table 2. (Continued).

	Values after four weeks of intervention <sup>a</sup>			Treatment effect <sup>b</sup>			
	Potassium <sup>c</sup>	Sodium	Placebo	Potassium vs. Placebo <sup>c</sup>	P	Sodium vs. Placebo	P
Renin ( $\mu\text{U/mL}$ )	16.1 (11.3-22.9)	6.1 (4.2-8.9)	11.5 (8.1-16.1)				
Ln renin ( $\mu\text{U/mL}$ )	2.78 $\pm$ 1.02	1.81 $\pm$ 1.08	2.44 $\pm$ 1.00	0.34 (0.08, 0.60)	0.01	-0.62 (-0.87, -0.36)	<0.001
Aldosterone (nmol/L)	0.24 (0.22-0.26)	0.18 (0.16-0.20)	0.21 (0.18-0.23)				
Ln aldosterone (nmol/L)	-1.44 $\pm$ 0.26	-1.72 $\pm$ 0.28	-1.58 $\pm$ 0.34	0.14 (0.07, 0.22)	<0.001	-0.14 (-0.22, -0.06)	<0.001
<b>Renal function parameters</b>							
Serum urea (mmol/L)	5.62 $\pm$ 1.41	5.16 $\pm$ 1.09	5.31 $\pm$ 1.13	0.30 (0.002, 0.59)	0.05	-0.15 (-0.44, 0.14)	0.3
Serum creatinine ( $\mu\text{mol/L}$ )	82.0 $\pm$ 12.8	77.5 $\pm$ 11.5	81.4 $\pm$ 13.3	0.5 (-2.0, 3.0)	0.7	-4.0 (-6.4, -1.6)	0.001
eGFR ( $\text{mL/min/1.73m}^2$ )	78.5 $\pm$ 11.7	82.7 $\pm$ 11.1	79.2 $\pm$ 11.6	-0.4 (-2.8, 1.9)	0.7	3.5 (1.2, 5.9)	0.003
ACR (mg/mmol)	0.33 (0.24-0.44)	0.47 (0.30-0.72)	0.47 (0.33-0.66)				
Ln ACR (mg/mmol)	-1.11 $\pm$ 0.86	-0.76 $\pm$ 1.25	-0.76 $\pm$ 1.00	-0.36 (-0.66, -0.06)	0.02	0.004 (-0.29, 0.30)	0.9

Abbreviations: ACR, urinary albumin to creatinine ratio; bpm, beats per minute; eGFR, estimated glomerular filtration rate.

<sup>a</sup> Data are presented as unadjusted mean  $\pm$  SD or geometric mean (95% CI).

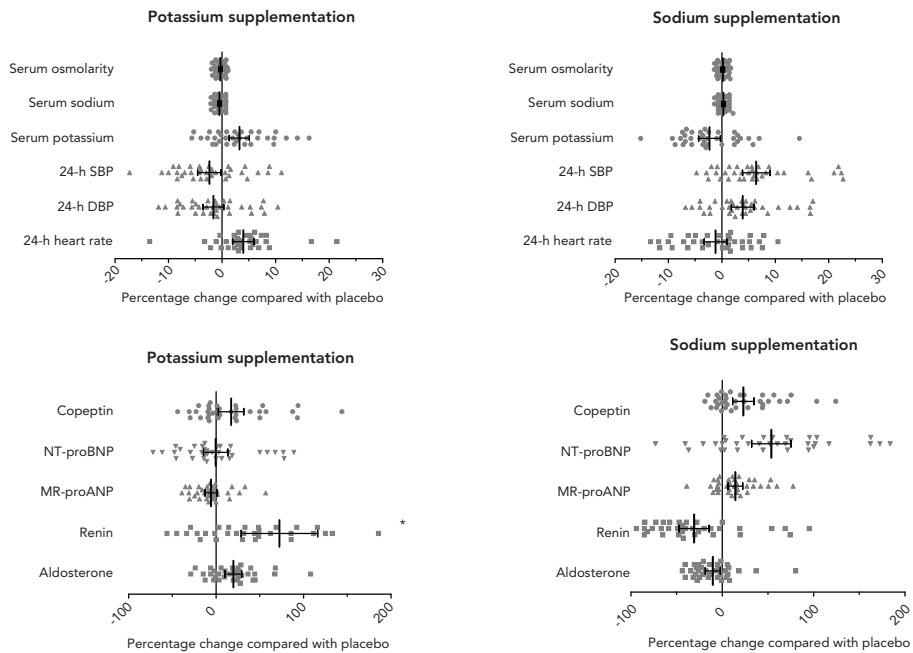
<sup>b</sup> Data are mean differences (95% CI) obtained from linear mixed-effect models.

<sup>c</sup> N = 34.

<sup>d</sup> To convert sodium in mmol/24 h to mg/24 h multiply by 23.

<sup>e</sup> To convert potassium in mmol/24 h to mg/24 h multiply by 39.

The percentage change in several markers for osmoregulation and volume regulation after potassium and sodium supplementation compared with placebo are depicted in Figure 1. Changes in serum osmolarity and serum sodium concentrations were minor (i.e., ranging between -2.0% and +1.7% for serum osmolarity and -2.1% and +2.1% for serum sodium; Figure 1). The percentage change in serum potassium, blood pressure, and heart rate were more pronounced and inter-individual variability was higher, but all percentage changes remained within the range of -20% to +25% (Figure 1). The changes in plasma copeptin, NT-proBNP, MR-proANP, renin, and aldosterone were much more pronounced, with distinct inter-individual differences (Figure 1).



**Figure 1.** Effects of potassium and sodium supplementation on markers of osmoregulation and volume regulation in 35 (pre)hypertensive subjects. \*3 data points (percentage change in renin after potassium supplementation of 281, 380, and 569%, respectively) are outside the x-axis limits.

## Discussion

The present study is, to the best of our knowledge, the first to investigate the humoral effects of potassium supplementation during sodium restriction and provides a biologically plausible explanation for the diminished blood pressure-lowering effects of potassium supplementation during sodium restriction. In this post-hoc analysis of a fully controlled dietary intervention study, we found that blood pressure decreased significantly after four weeks of potassium supplementation, indicating that potassium has blood pressure-lowering effects, albeit relatively small, during sodium-restriction. The blood pressure-lowering effects of potassium during sodium restriction seem mitigated by activation of several counter regulatory mechanisms (i.e., increased secretion of vasopressin, stimulation of RAAS, and increased heart rate) in order to maintain volume homeostasis and counterbalance the decrease in blood pressure.

The blood pressure-lowering effects of potassium have been established in several randomized clinical trials (6,14). Potassium is suggested to exert its blood pressure-lowering effects, at least in part, through stimulation of natriuresis (20,21). A dietary potassium load was reported to induce a rapid natriuresis (22,23), which is most likely explained by deactivation of the NaCl cotransporter that occurs independent of plasma aldosterone concentrations (23). Moreover, potassium was reported to be more effective in reducing blood pressure at higher levels of sodium intake (6,11). High potassium intake is suggested to blunt the blood pressure increasing effects of high sodium intake (24), which could be explained by enhanced natriuretic effects of potassium during high sodium intake (22). A previous randomized crossover trial that examined the effects of increased potassium intake on top of a low sodium diet (i.e., 70 mmol/24 h) showed little or no effect of potassium on blood pressure in subjects with mild or moderate hypertension (13). It was hypothesized that potassium has either less of a natriuretic effect or less effect on renin suppression when sodium intake is restricted (13). In the present study, we found a significant decrease in blood pressure after potassium supplementation, indicating that potassium can have blood pressure-lowering effects when sodium intake is restricted. Because the blood pressure-lowering effects of potassium are suggested to depend on the level of sodium intake (6,11), differences in background sodium intake (i.e., ~100 mmol/24 h in the present study versus ~70 mmol/24 h in the study of Smith et al. (13)) may explain the differences in the observed effects of potassium supplementation on blood pressure.

Interestingly, the blood pressure-lowering effects of potassium during sodium restriction seem mitigated by counter regulatory effects of hormones involved in maintenance of volume and blood pressure homeostasis. In line, we found significant

increases in both plasma renin and aldosterone. In hyperkalemia, aldosterone secretion is increased, while secretion of renin and angiotensin II is suppressed, resulting in electrochemical sodium reabsorption that promotes kaliuresis (25). In contrast, secretion of both renin and aldosterone is increased in effective circulating volume depletion, in which aldosterone and angiotensin II act synergistically to promote maximal sodium reabsorption (25). The significant increase in serum urea is likely to correspond with increased tubular sodium reabsorption, because reabsorption of filtered urea is passively linked to that of sodium and water (7). In addition, we found a significant increase in plasma copeptin, a surrogate for vasopressin. Vasopressin stimulates water reabsorption, which raises the extracellular volume towards normal (17). Furthermore, we found a significant increase in 24-h heart rate, which may indicate that the decrease in effective circulating volume is counterbalanced by an increase in heart rate to increase cardiac output.

The effects of increased sodium intake on RAAS and natriuretic peptides are well known. In line with previous studies, we found that increased sodium intake is associated with suppression of RAAS (26,27) and increases in natriuretic peptides (7,26). However, limited data are available on the effects of increased dietary sodium intake on copeptin, or vasopressin, concentrations. In line with a recent study of Tasevska *et al.* (28), we found that increased sodium intake was associated with an increase in plasma copeptin concentrations.

We found that percentage changes in serum sodium concentration after sodium and potassium supplementation, compared to placebo, are minor (i.e., less than 2%). This suggests that, in line with a recent study of Zhang *et al.* (29), serum sodium concentrations are tightly regulated around a subject-specific set point.

We acknowledge that this study has several limitations. The main limitation of the present study is the relatively small sample size. However, the fact that we found anticipated effects of sodium supplementation and opposing effects of potassium supplementation makes our data robust. Furthermore, we studied relatively short-term effects of potassium and sodium supplementation on osmoregulation and volume regulation in (pre)hypertensive subjects. It would be of interest to investigate the long-term effects of potassium and sodium intake on osmoregulation and volume regulation and the risk of cardiovascular and renal disease end points. A major strength of our study is the fully controlled diet, which strongly reduced the intraindividual variability resulting from dietary influences (e.g., use of alcohol, coffee, and salt) and thereby increasing the power to demonstrate effects that are exclusively attributable to potassium and sodium intake. The power of our study is furthermore strengthened by its design as a cross-over study, allowing paired data analysis.

In conclusion, in this post-hoc analysis of a fully controlled dietary intervention study, we demonstrated that potassium has blood pressure-lowering effects during sodium restriction. These blood pressure-lowering effects of potassium, however, seem mitigated by activation of several counter regulatory mechanisms (i.e., increased secretion of vasopressin, stimulation of RAAS, and increased heart rate) to maintain volume homeostasis and counterbalance the decrease in blood pressure. Our study provides biological plausibility for the observation that blood pressure-lowering effects of potassium supplementation are diminished during sodium restriction.

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