© 2015 International Society of Nephrology

Evidence for a gastrointestinal–renal kaliuretic signaling axis in humans

Richard A. Preston[1,2,3], David Afshartous[1], Rolando Rodco[1], Alberto B. Alonso[1] and Dyal Garg[1]

[1]Clinical Pharmacology Research Unit (CPRU), Division of Clinical Pharmacology, Department of Medicine, Miller School of Medicine, University of Miami, Miami, Florida, USA; [2]Department of Cellular Biology and Pharmacology, Herbert Wertheim College of Medicine, Florida International University, Miami, Florida, USA and [3]Clinical Pharmacology Research Unit (CPRU), Division of Clinical Pharmacology, Department of Medicine, Miller School of Medicine, University of Miami, Jackson Memorial Hospital, Miami, Florida, USA

A gastrointestinal–renal kaliuretic signaling axis has been proposed to regulate potassium excretion in response to acute potassium ingestion independent of the extracellular potassium concentration and aldosterone. Here we studied this presumed axis in 32 individuals in our clinical pharmacology unit while on a 20 mmol sodium and 60 mmol potassium diet. The serum potassium concentration, potassium excretion, aldosterone, and insulin were measured following either a 35 mmol oral potassium load, a potassium- and sodium-deficient complex meal, or a potassium-deficient complex meal plus 35 mmol potassium. This design allowed determination of the component effects on potassium handling of the meal and potassium load separately. The meal plus potassium test was repeated following aldosterone blockade with eplerenone to specifically evaluate the role of aldosterone. In response to the potassium-deficient meal plus 35 mmol potassium, the serum potassium did not increase but the hourly mean potassium excretion increased sharply. This kaliuresis persisted following aldosterone blockade with eplerenone, further suggesting independence from aldosterone. Thus, a gastrointestinal–renal kaliuretic signaling axis exists in humans mediating potassium excretion independent of changes in the serum potassium concentration and aldosterone. The implication of this mechanism is yet to be determined but may account for a significant component of potassium excretion following a complex potassium-rich meal.

Kidney International advance online publication, 26 August 2015; doi:10.1038/ki.2015.243

KEYWORDS: distal tubule; potassium channels; signaling

Correspondence: *Richard A. Preston, Clinical Pharmacology Research Unit, Division of Clinical Pharmacology, Department of Medicine, Miller School of Medicine, University of Miami, 1500 NW 12th Avenue, 15th Floor West Tower, Miami, Florida 33136, USA. E-mail: rpreston@med.miami.edu*

Received 22 December 2014; revised 18 June 2015; accepted 18 June 2015

Regulation of renal potassium excretion is currently attributed to two independent control mechanisms.[1–3] The first mechanism is a long-recognized and well-characterized feedback system,[4–7] in which the extracellular potassium concentration is believed to be the main determinant of potassium excretion following a potassium-containing meal. The increase in extracellular potassium concentration directly increases renal potassium excretion and also stimulates aldosterone secretion, which further amplifies kaliuresis, thereby constituting a negative feedback system.

Less well recognized but gaining acceptance[1–3] is a 'feed-forward' gastrointestinal (GI)–renal kaliuretic signaling axis that directly increases renal potassium excretion, independent of increases in extracellular potassium concentration and aldosterone.[8–20] This axis is hypothesized to be mediated by sensors located in the GI tract or portal circulation that detect ingested potassium and rapidly initiate the release or activation of unknown mechanism(s) that produce an acute increase in renal potassium excretion.[8–20] The feedback and feed-forward mechanisms are believed to act concurrently.

The central objective of this study was to investigate the existence and magnitude of this purported GI–renal kaliuretic signaling axis in humans. We also sought to investigate the integrated effects of serum potassium concentration, aldosterone, and insulin in mediating acute cellular translocation and renal excretion of potassium. We conducted potassium handling experiments[21–24] in two groups of healthy human volunteers. Group 1 ($N=20$) completed a 10-day confinement period in our clinical pharmacology research unit throughout which all subjects received a 20 mmol/day sodium and 60 mmol/day potassium diet. We determined the acute time course of serum potassium concentration (mmol/l) and renal potassium excretion (U_KV, mmol/h) following three potassium handling experiments: (i) 35 mmol oral potassium load alone (KCl), (ii) potassium- and sodium-deficient meal alone (Meal), and (iii) 35 mmol oral potassium load plus potassium- and sodium-deficient meal (Meal+KCl). The Meal+KCl experiment was designed to approximate the normal physiologic condition in which a complex potassium-containing meal is consumed.

Following the Meal+KCl experiment, we observed a substantial kaliuresis that occurred in the absence of an

Table 1 | Baseline and demographic characteristics mean (s.d.)

	Age (years)	Gender	Race	Ethnicity	BMI	MDRD	C-GAULT	SBP	DBP
Group 1 ($N=20$)	43.6 (18.1)	11 F/9 M	18 W/2 B	19 H/1 AA	27.2 (3.1)	111 (24)	121 (32)	122 (11)	78 (5)
Group 2 ($N=12$)	41.1 (18.0)	7 F/5 M	12 W	12 H	27.0 (2.2)	136 (58)	158 (60)	118 (7)	76 (4)

Abbreviations: AA, African American; B, Black; BMI, body mass index; C-GAULT, Cockcroft-Gault Equation estimated glomerular filtration rate (ml/min); DBP, diastolic blood pressure (mmHg); F, female; H, Hispanic; M, male; MDRD, Modification of Diet in Renal Disease estimated glomerular filtration rate; SBP, systolic blood pressure (mm Hg); W, white.

increase in serum potassium. We replicated the Meal+KCl experiment in Group 2 ($N=12$) following aldosterone blockade with eplerenone 400 mg to specifically evaluate the contribution of aldosterone to this kaliuresis. We again observed a kaliuresis that was similar in magnitude to that observed in the original Meal+KCl experiment. These combined results suggest that the kaliuresis we observed with the Meal+KCl experiment is independent of both serum potassium and aldosterone concentration. Our results support a feed-forward GI–renal kaliuretic signaling axis in humans that is independent of serum potassium concentration and aldosterone and may account for a substantial proportion of the potassium excretion that follows a complex potassium-containing meal.

RESULTS

Baseline and demographic characteristics

Group 1 consisted of 20 participants who completed all phases of the randomized study including all three potassium handling studies (Table 1). Group 2 consisted of 12 additional participants who completed the Meal+KCl experiment following aldosterone blockade with eplerenone 400 mg. There were 18 women and 14 men in the study. All subjects were in generally good health, although 15 out of 20 in Group 1 and 9 out of 12 in Group 2 were either obese or overweight. The mean body mass index was 27.2 for Group 1 and 27.0 for Group 2. All participants except one were Hispanic. No subjects were receiving regular medications. All subjects were confined for 10 days in the clinical pharmacology research unit and received a 20 mmol sodium/day, 60 mmol potassium/day diet throughout the entire 10-day period.

Changes in serum potassium concentration

Following 35 mmol oral KCl alone (KCl), mean serum potassium concentration increased sharply from baseline 4.52 (95% confidence interval: 4.401, 4.62) to a peak 5.03 (4.81, 5.25; $P<0.001$) mmol/l at 30 min, remained elevated until 90 min then gradually returned toward baseline concentration (Figure 1). In contrast, with the potassium- and sodium-deficient meal alone (Meal), potassium concentration *decreased* from baseline 4.54 (4.31, 4.76) to 3.90 (3.78, 4.01; $P<0.001$) mmol/l at 60 min and remained depressed. With 35 mmol oral potassium plus potassium- and sodium-deficient meal (Meal+KCl), serum potassium concentration did not increase at any time point during the 5-h study period. Mean serum potassium concentration decreased to a nadir of 4.30 mmol/l (4.13, 4.46) at 60 min.

Potassium excretion

Following KCl alone mean potassium excretion (U_KV) rapidly increased from baseline to a peak 10.0 (8.24, 11.75 $P<0.001$) mmol/h at 60 min then returned toward baseline (Figure 2). In contrast with Meal alone, U_KV decreased from baseline to 1.84 (1.63, 2.04; $P=0.002$) mmol/h at 120 min.

Following Meal+KCl, U_KV increased from baseline 2.54 (2.14, 2.94) mmol/h to a peak of 5.14 (3.67, 6.60; $P<0.001$) mmol/h at 60 min and remained elevated. This substantial kaliuresis occurred during the first hour without a corresponding increase in serum potassium concentration. This indicates that potassium excretion following Meal+KCl, the condition designed to approximate the actual physiologic situation in which a potassium-containing meal is ingested, was independent of changes in serum potassium concentration.

Cumulative potassium excretion

Cumulative potassium excretion increased rapidly and reached 40.24 (36.22, 44.27) mmol following KCl alone (Figure 3). Despite no increase in serum potassium concentration at any time point following Meal+KCl, we observed a substantial cumulative potassium excretion that reached 26.43 (22.36, 30.50) mmol, whereas cumulative excretion following Meal alone reached only 16.51 (14.41, 18.61) mmol. Differences between groups were assessed via analysis of variance. All pairwise comparisons of cumulative potassium excretion among the three experiments were statistically significant ($P<0.001$) including the comparison of Meal vs. Meal+KCl.

Plasma aldosterone

Following 4 days of 20 mmol sodium and 60 mmol potassium diet, baseline plasma aldosterone (PA) was elevated, probably due to mild volume depletion induced by the low-sodium diet (Figure 4). In response to KCl alone, in which serum potassium concentration increased rapidly and substantially, PA rapidly reached a peak of 32.1 (24.88, 39.32; $P<0.001$) ng/dl at 30 min (Figure 4). With Meal alone, PA did not increase at any point throughout the study. Following Meal+KCl, mean PA demonstrated a small increase to 25.85 at 30 min. Given that serum potassium concentration did not increase with the Meal+KCl experiment, we conducted secondary analyses to investigate the potential role of the small increase in aldosterone with respect to the kaliuresis. The Pearson correlation between the total potassium excreted and the area-under-the-curve for PA was $r=-0.06$ (−0.38, 0.50; $P=0.77$). Moreover, post-baseline hourly correlations of U_KV with corresponding hourly midpoints of PA were not statistically

Download English Version:

https://daneshyari.com/en/article/6161876

Download Persian Version:

https://daneshyari.com/article/6161876

Daneshyari.com