Evidence for gut factor in K⁺ homeostasis

Felix N. Lee, Gisuk Oh, Alicia A. McDonough, and Jang H. Youn

Department of Physiology and Biophysics, Keck School of Medicine, University of Southern California, Los Angeles, California

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Lee FN, Oh G, McDonough AA, Youn JH. Evidence for gut factor in K⁺ homeostasis. Am J Physiol Renal Physiol 293: F541–F547, 2007. First published May 23, 2007; doi:10.1152/ajprenal.00427.2006.—We tested the hypothesis that K⁺ intake is sensed by putative K⁺ sensors in the splanchnic areas, and renal K⁺ handling is regulated by this signal. K⁺ was infused for 2 h into overnight-fasted rats via the jugular vein (systemic infusion), hepatic portal vein (intraportal infusion), or stomach (intragastric infusion) (n = 5 each), and plasma K⁺ concentration ([K⁺]) and renal K⁺ excretion were measured during the 2-h preinfusion, 2-h K⁺ infusion, and 3-h washout periods. During systemic K⁺ infusion, plasma [K⁺] increased by ∼1.3 mM (P < 0.05), and, on cessation of the K⁺ infusion, plasma [K⁺] fell to the preinfusion level within 1–2 h. Renal K⁺ excretion changed in proportion to the changes in plasma [K⁺]. During intraportal or intragastric K⁺ infusion, plasma [K⁺] and renal K⁺ excretion profiles were similar to those with systemic infusion. The effects of K⁺ infusions via different routes (n = 5 or 6 each) were also studied during simultaneous feeding of overnight-fasted rats with a K⁺-deficient diet. During the meal, intraportal infusion resulted in increases in plasma [K⁺] similar to those with the systemic K⁺ infusion, while intragastric K⁺ infusion did not significantly increase plasma [K⁺]. When the intragastric K⁺ infusion was combined with a meal, there was marked enhancement of clearance of the K⁺ infused, which was associated with an apparent increase in renal efficiency of K⁺ excretion. These data suggest that there may be a gut factor that enhances renal efficiency of K⁺ excretion during meal (or dietary K⁺) intake.

feedback control; feedforward control; potassium sensor; potassium excretion

EXTRACELLULAR K⁺ concentration ([K⁺]) is maintained within a narrow range in mammals, and this is critical for normal membrane potentials and cell functions (1, 12). Extracellular K⁺ homeostasis relies on the maintenance of total body K⁺ content and distribution of K⁺ between intracellular and extracellular spaces. Total body K⁺ content is maintained by a continuous balance between dietary intake and excretion of K⁺. The kidneys are responsible for ∼90% of K⁺ excretion and have a remarkable capacity to regulate K⁺ excretion to match K⁺ intake (1, 21). Thus the kidneys play a predominant role in the maintenance of chronic K⁺ balance. In addition, extrarenal tissues, mainly liver and skeletal muscle, provide K⁺ buffering capacity by shifting K⁺ between intracellular and extracellular spaces. Since the adaptation of the kidneys to altered K⁺ balance is slow (5), the K⁺ buffering capacity of extrarenal tissues is critically important in the acute regulation of extracellular K⁺ (1, 12).

According to the traditional view, extracellular [K⁺] is the major factor in the regulation of renal K⁺ excretion (8, 9).

Extracellular [K⁺] increases during dietary K⁺ intake, and this increase stimulates renal K⁺ secretion by a direct action on K⁺ excretion in the collecting duct (9). In addition, increased extracellular [K⁺] stimulates aldosterone secretion, which would further stimulate renal K⁺ excretion (16, 17). Increased renal K⁺ excretion will then help to normalize extracellular [K⁺]. Thus the maintenance of K⁺ homeostasis has been traditionally understood based on the concept of negative feedback control (Fig. 1). However, Rabinowitz (16, 17) challenged this traditional view. He pointed out that plasma K⁺ and aldosterone can stimulate renal K⁺ excretion only at levels above their normal ranges (2, 19, 23, 24). In his studies in the sheep (18), meal intake produced a pronounced kaliuresis, which was accompanied by no change in plasma aldosterone concentration. Plasma [K⁺] increased during meal intake, but the increase was only 0.5 meq/l, which was too small (when reproduced by intravenous K⁺ infusion) to account for the meal-induced kaliuresis (19). Thus the meal-induced kaliuresis could not be explained by changes in plasma K⁺ or aldosterone concentration. To explain the increase in renal K⁺ excretion following meal (i.e., K⁺) intake, he proposed a kaliuretic reflex arising from sensors in the splanchnic bed (i.e., gut, portal circulation, and/or liver). According to this proposal, renal K⁺ excretion can be increased, without (or before) increases in extracellular [K⁺], by a mechanism controlled by sensing of K⁺ intake (i.e., sensing of local increases in [K⁺] in splanchnic areas during K⁺ intake). Thus a new concept of feedforward control has been proposed (Fig. 1). This idea was supported by the study of Morita et al. (14), which demonstrated that an intraportal injection of KCl in rats increased hepatic afferent nerve activity (HANA), suggesting a hepatoportal mechanism that senses the portal venous [K⁺]. However, the mode of K⁺ administration (e.g., injection) in the Morita et al. study was not physiological, which undermines the physiological significance of the proposed hepatoportal mechanism (see DISCUSSION).

In the present study, we attempted to test the hypothesis that K⁺ intake is sensed by K⁺ sensors in the gut, portal vein (PV), and/or liver, and renal K⁺ excretion is regulated by this signal. To achieve this goal, we employed strategies similar to those used to demonstrate the presence of PV glucose sensors in rats, i.e., the “local irrigation” technique (6, 10): K⁺ was infused for 2 h into the stomach, the hepatic PV, or a systemic vein, and its impact on plasma [K⁺] and renal K⁺ excretion was measured. Our results indicate that, during fasting, the K⁺ infusions via the different routes resulted in similar profiles of plasma [K⁺] and renal K⁺ excretion. Interestingly, when simultaneously fed a K⁺-deficient diet, the intragastric (IG), but not the intraportal,
Feedback control

K⁺ Intake → K⁺ + Renal Excretion

Feedforward control

K⁺ Intake → K⁺ + Renal Excretion

Fig. 1. Schematic diagrams illustrating control of extracellular fluid (ECF) K⁺ concentration ([K⁺]) via the classic feedback and hypothetical feedforward mechanisms.

K⁺ infusion enhanced the efficiency of renal K⁺ excretion and prevented significant rises in plasma [K⁺] during the K⁺ infusion. These data suggest the existence of a gut factor in the regulation of renal K⁺ excretion during dietary K⁺ intake. Evidence supporting a role for hepatoporal factors was not obtained.

METHODS

Animals and surgical procedures. Male Wistar rats weighing 250–300 g were obtained from Simonsen (Gilroy, CA) and housed under controlled temperature (22 ± 2°C) and lighting (12 h light, 0600-1800; 12 h dark, 1800-0600), with free access to water and standard rat chow. One week before the experiment, rats were chronically cannulated either in the jugular vein (JV), the hepatic PV, or the stomach. Surgeries were performed under single-dose anesthesia (3:1 ketamine HCl, xylazine, acepromazine maleate; 0.1 ml/100 g body wt ip). Cannulas were placed in the JV [Silastic, 0.012-cm inner diameter (ID)] or the hepatic PV via the superior mesenteric vein (Silastic, 0.03 cm ID), as described by Hevener et al. (10). Gastric cannula (Silastic, 0.076 cm ID) was implanted in the forestomach, as described by Tsukamoto et al. (22). All cannulas were tunneled subcutaneously and exteriorized at the back of the neck. Animals were placed in individual cages, and spring coils and swivels were used for the protection of cannulas and free movement of animals within the cages. Patency for IG cannula was maintained with a constant infusion of distilled water (~0.5 ml/h), while jugular and PV cannulas were flushed with heparinized saline (50 U/ml) twice weekly. In addition, at least 4 days before the experiment, the animals were placed in tail restraint as previously described (3, 4) to protect a tail arterial catheter for blood sampling, which was placed in the morning of the experiment (i.e., ~0600). Animals were free to move about and allowed unrestricted access to food and water. All procedures were approved by the Institutional Animal Care and Use Committee at the University of Southern California.

Experimental protocols. In study 1, the effects of K⁺ infusion on plasma [K⁺] and renal K⁺ excretion were studied in conscious overnight-fasted rats. Food was removed at 1700 on the day before the experiment, and the experiments were started at 0900. Each experiment consisted of three periods: 2-h preinfusion, 2-h KCl infusion, and 3-h washout periods. K⁺ was infused into the stomach (IG), PV ("intraportal"), or JV ("systemic") to test the presence of the putative K⁺ sensors in the splanchnic bed. The rationale of this design was that, if K⁺ sensors (and subsequent regulation of [K⁺] by this signal) exist in the splanchnic bed, the impact of each K⁺ infusion on plasma [K⁺] and renal K⁺ excretion would be different, depending on the location of sensors and the route of K⁺ infusion (see Fig. 2). K⁺ was infused as 300 mM KCl (19) at a rate of 100 mg·kg⁻¹·h⁻¹ (or ~2.5 ml/h of 300 mM KCl) (n = 5 each). Blood samples were collected for determination of plasma [K⁺] at variable intervals during the 2-h preinfusion, 2-h K⁺ infusion, and 3-h washout periods. Urinary K⁺ excretion was determined by collecting urine every hour throughout the experiment using specially designed cages. The animal cages had wire floor but were open at the bottom and were placed on an aluminum tray. The tray was replaced every hour to collect urine passed. To avoid the contamination of urine passed by fecal K⁺, a mesh screen was placed underneath the wire floor to separate feces from urine passed. To obtain a constant flow of urine, animals were infused with a constant volume (4 ml/h) of fluid (saline or saline + KCl during the K⁺ infusion period) throughout the experiment. This volume infusion did not appear to affect K⁺ excretion, as the baseline K⁺ excretion rate was indistinguishable from the basal rate of K⁺ excretion estimated without fluid infusion by measuring K⁺ in the urine collected during the light phase (i.e., between 7 AM and 7 PM) without food (data not shown). Each animal was used for only one

Fig. 2. Schematic diagrams illustrating the sensing of K⁺ entry via different K⁺ infusion sites by hypothetical K⁺ sensors in the gut, portal vein, and liver. Intragastric (IG) K⁺ delivery (left) would be sensed by all of the sensors, whereas systemic K⁺ delivery (right) may not be directly sensed by any of the splanchnic K⁺ sensors. Middle: intraportal K⁺ delivery may be sensed by the portal vein (PV) and hepatic K⁺ sensors.
experiment and killed by an overdose of pentobarbital sodium at the end of the experiment.

In study 2, the effects of K⁺ infusion on plasma [K⁺] and renal K⁺ excretion were studied during feeding of overnight-fasted rats. Experiments were performed exactly the same as those in study 1, except that animals were fed with a K⁺-deficient diet (TD 88239; Harlan Teklad, Madison, WI) during the K⁺ infusions (i.e., systemic, intraportal, and IG; n = 5 or 6 each). Thus, following the 2-h preinfusion period, the animals were given the diet, and the K⁺ infusions were started immediately. Since the animals were fasted overnight, they usually started to eat right away when food was given.

**Determination of plasma and urine [K⁺] and gastric K⁺ contents.** Plasma and urine K⁺ levels were determined by flame photometry using a Radiometer FLM 3 flame photometer, as previously reported (4). In some experiments, K⁺ content was determined in the stomach and the small and large intestines by collecting and homogenizing luminal contents of these organs and measuring K⁺.

**Calculations.** Basal rate of urinary K⁺ excretion was calculated by averaging the values determined hourly during the 2-h preinfusion period. Increases in urinary K⁺ excretion (ΔUₑ) were calculated as the sum of urinary K⁺ excretions during the 2-h K⁺ infusion and the 3-h washout periods minus the 5-h equivalent of basal K⁺ excretion (i.e., basal K⁺ excretion × 5 h). Basal plasma [K⁺] was also determined during the preinfusion period. In some experiments, plasma [K⁺] decreased below or increased above the preinfusion basal level at the end of the experiments, although, on average, the final hour plasma [K⁺] was not different from the preinfusion values. Therefore, basal plasma [K⁺] was calculated as the average of the preinfusion and final-hour plasma [K⁺], and this helped to reduce the variations in the estimation of area under the [K⁺] curve above basal (ΔAUCkB) (see below). Total area under the plasma [K⁺] curve was calculated using the trapezoidal method during the 2-h K⁺ infusion and the 3-h washout periods. ΔAUCkB was then calculated by subtracting the area under the baseline (i.e., basal plasma [K⁺] × 5 h) from total area under the plasma [K⁺] curve.

**Statistical analysis.** Data are expressed as means ± SE. The significance of the differences in mean values among different treatment groups was evaluated using one-way or two-way ANOVA followed by ad hoc analysis using the Newman-Keuls’ multiple-range test. Differences were considered significant at P < 0.05.

**RESULTS**

**Time course changes in plasma [K⁺] during the systemic, intraportal, and IG K⁺ infusions in the fasting state.** During systemic K⁺ infusion (via the JV), plasma [K⁺] increased by ~1.3 mM, that is, from the preinfusion baseline of 3.8 ± 0.1 to 5.1 ± 0.1 mM during the second hour of the K⁺ infusion (Fig. 3A). On cessation of the K⁺ infusion, plasma [K⁺] fell to the preinfusion level within 1–2 h. The average plasma [K⁺] during the final hour, i.e., between 2 and 3 h after the cessation of the K⁺ infusion, was identical to the preinfusion baseline, indicating that the infused K⁺ was completely disposed during the 2-h K⁺ infusion and the subsequent 3-h washout periods. During intraportal K⁺ infusion, the plasma [K⁺] profile was virtually identical to that with the systemic infusion, except that the changes were slightly slower (Fig. 3A). This difference might be due to a buffering capacity of the liver to take up K⁺ during the K⁺ infusion and release it into the blood during the subsequent washout period. When K⁺ was infused into the stomach (IG infusion), plasma [K⁺] rose rapidly and showed a profile similar to that with the systemic infusion, except that the changes were slightly slower (Fig. 3B). This difference might be due to a buffering capacity of the liver to take up K⁺ during the K⁺ infusion and release it into the blood during the subsequent washout period. When K⁺ was infused into the stomach (IG infusion), plasma [K⁺] rose rapidly and showed a profile similar to that with the systemic infusion, indicating that K⁺ absorption from the stomach (or gut) was extremely fast.

**Fig. 3.** Time courses of plasma [K⁺] (A and B) and renal K⁺ excretion (C and D) and total K⁺ excretion (0–300 min; E) with the systemic (jugular vein (JV)), intraportal (PV), and IG K⁺ infusion (KINF) in overnight-fasted rats. The time course data were compared between the systemic vs. the intraportal (A and C) or the systemic vs. the IG (B and D) K⁺ infusion. Values are means ± SE for 5 experiments.
Time course changes in renal $[K^+]$ excretion during the systemic, intraportal, and IG $K^+$ infusions in the fasting state. Renal $K^+$ excretion was determined at every hour during the 2-h preinfusion, 2-h $K^+$ infusion, and 3-h washout periods. The baseline values were stable during the preinfusion period (Fig. 3C). During the systemic $K^+$ infusion, urinary $K^+$ excretion increased as plasma $[K^+]$ increased. The increase was greater in the second than in the first hour of $K^+$ infusion, in proportion to the average values of plasma $[K^+]$ during the hours. When $K^+$ infusion was stopped, renal $K^+$ excretion slowly decreased and returned to preinfusion baseline by the end of the 3-h washout period. The intraportal and the IG $K^+$ infusions also produced renal $K^+$ excretion profiles similar to that with the systemic $K^+$ infusion. The total amount of renal $K^+$ excretion during the 2-h $K^+$ infusion and the subsequent 3-h washout periods was not different among the three $K^+$ infusion groups ($P > 0.05$). Thus, when studied in the fasting state, intraportal or IG $K^+$ infusion did not increase renal $K^+$ excretion beyond that provoked by systemic $K^+$ infusion.

Time course changes in plasma $[K^+]$ and renal $K^+$ excretion during the systemic, intraportal, and IG $K^+$ infusions with a $K^+$-deficient meal. The effects of the $K^+$ infusions via different routes were also studied during feeding of overnight-fasted rats with a $K^+$-deficient diet to examine potential signals stimulated by ingesting a meal with the $K^+$, the normal route of $K^+$ intake. Compared with the fasting state, the rise in plasma $[K^+]$ during the $K^+$ infusion, regardless of route of administration, was smaller when the $K^+$ infusion was combined with a meal (Fig. 4). The rise in plasma $[K^+]$ was suppressed the greatest with the IG $K^+$ infusion: plasma $[K^+]$ increased in only two of the five animals studied; thus there was not a significant increase in average plasma $[K^+]$ in the IG $K^+$ infusion + $K^+$-deficient meal group ($P > 0.05$). Renal $K^+$ excretion was not much different between the fasting vs. meal groups in the systemic and intraportal infusion groups ($P > 0.05$). However, in the IG $K^+$ infusion group, renal $K^+$ excretion during the 2-h $K^+$ infusion period was significantly reduced with a meal vs. infusion during the fasting state ($P < 0.05$), presumably due to the lack of significant increases in plasma $[K^+]$. However, it is important to note that renal $K^+$ excretion was substantially elevated above basal, especially during the washout period, despite the fact that plasma $[K^+]$ was not significantly different from preinfusion baselines (Fig. 5). In the three animals in which no increase in plasma $[K^+]$ occurred, renal $K^+$ excretion was increased significantly above basal ($570 \pm 12 \mu$mol, $P < 0.01$), suggesting the presence of an IG factor that is regulated independent of plasma $K^+$ that stimulates renal $K^+$ excretion. This is further supported by the finding that the pattern of changes (i.e., continued increases) in renal $K^+$ excretion after the termination of IG $K^+$ infusion was clearly different from that with other infusions, where renal $K^+$ excretion fell, together with plasma $[K^+]$, immediately after the termination of $K^+$ infusion (Fig. 4).

Relationship between increases in plasma $[K^+]$ vs. renal $K^+$ excretion. The increase in plasma $[K^+]$, expressed as $\Delta$AUC$_K$ (0–300 min; see METHODS), was similar during the systemic, intraportal, and IG $K^+$ infusion when studied in the fasting state (Fig. 6A). A $K^+$-deficient meal was combined with the $K^+$ infusion, $\Delta$AUC$_K$ was significantly reduced, especially in the IG $K^+$ infusion ($P < 0.05$). In this case, $\Delta$AUC$_K$ was significantly smaller than that with the IG infusion in the fasting state or other infusions during a meal ($P < 0.05$). In fact, $\Delta$AUC$_K$ in the IG infusion during a meal was not statistically different from zero ($P > 0.05$). Urinary $K^+$ excretion above the baseline ($\Delta$U$_K$) for the 5-h $K^+$ infusion and washout period was similar among the different $K^+$ infusions in the fasting state or during a meal (Fig. 6B). Unlike $\Delta$AUC$_K$, a meal did not significantly affect $\Delta$U$_K$ ($P > 0.05$). Figure 6C shows the relationship between $\Delta$U$_K$ and $\Delta$AUC$_K$ under each experimental condition. The ratio of $\Delta$U$_K$ to $\Delta$AUC$_K$ may indicate the efficiency of the kidneys to increase $K^+$ excretion in response to increases in plasma $[K^+]$. This ratio was notably increased with IG $K^+$ infusion during a meal,

![Fig. 4. Time courses of plasma $[K^+]$ (A, B, and C) and renal $K^+$ excretion (D, E, and F) with the systemic (left), intraportal (middle), and IG (right) $K^+$ infusions during a $K^+$-deficient meal compared with the data obtained in the overnight-fasting state (Fig. 3). Values are means ± SE for 5 or 6 experiments.](http://ajprenal.physiology.org/)
compared with other infusions during a meal or the same IG infusion in the fasting state. These data indicate that renal efficiency was markedly increased when K\textsuperscript+ enters the stomach with a meal, which is the normal situation of K\textsuperscript+ intake.

Absorption of K\textsuperscript+ from the stomach. In a separate series, we determined the degree of absorption of K\textsuperscript+ that enters the stomach with a meal within our experimental time frame, i.e., a total of 5 h, consisting of the 2-h refeeding and subsequent 3-h follow-up periods. In this series, overnight-fasted rats were fed for 2 h with diet containing normal (1%) or no K\textsuperscript+, and K\textsuperscript+ content was determined in the stomach and small and large intestines 3 h after the refeeding period. Table 1 summarizes that K\textsuperscript+ content was different in the stomachs of 1% vs. no K\textsuperscript+ diet groups, but not different in the small and large intestines between the two groups. The difference in K\textsuperscript+ content in the stomach was calculated to be ~15% of K\textsuperscript+ intake in the 1% K\textsuperscript+ diet group, indicating that nearly all (~85%) of the dietary K\textsuperscript+ was absorbed during the 2-h refeeding and the subsequent 3-h follow-up periods.

**DISCUSSION**

Our study was designed to test the hypothesis that K\textsuperscript+ intake is sensed by the putative K\textsuperscript+ sensors in the splanchnic areas, and that renal K\textsuperscript+ handling is regulated by this signal. To accomplish the aim, K\textsuperscript+ was infused for 2 h into the stomach, the hepatic PV, or a systemic vein, and plasma [K\textsuperscript+] and renal K\textsuperscript+ excretion were measured before, during, and after the K\textsuperscript+ infusion. Our results indicate that the K\textsuperscript+ infusions via the different routes resulted in similar profiles of plasma [K\textsuperscript+] and renal K\textsuperscript+ excretion when studied in the fasting state. However, the route of K\textsuperscript+ infusion had a dramatic effect on plasma [K\textsuperscript+] when rats were simultaneously fed a K\textsuperscript+-deficient diet. While intraportal infusion resulted in increases in plasma [K\textsuperscript+] similar to those with the systemic K\textsuperscript+ infusion, the IG K\textsuperscript+ infusion did not significantly increase plasma [K\textsuperscript+], yet still provoked a significant increase in renal K\textsuperscript+ excretion. Thus, when the IG K\textsuperscript+ infusion was combined with a meal, there appeared to be marked enhancement of clearance of the K\textsuperscript+ infused, which was associated with an apparent increase in renal efficiency of K\textsuperscript+ excretion (see below). These data suggest that there may be a gut factor that enhances renal efficiency of K\textsuperscript+ excretion during meal (or dietary K\textsuperscript+) intake.

In the fasting state, the IG K\textsuperscript+ infusion produced a profile of plasma [K\textsuperscript+] identical to that with the intraportal K\textsuperscript+ infusion, indicating that K\textsuperscript+ absorption from the gut was very fast with an empty stomach. However, when the stomach is filled with food during a meal, the K\textsuperscript+ infused might be retained by the food, and K\textsuperscript+ absorption might be slowed. Therefore, it may be
conceivable that a slow absorption of K⁺ from the gut (or delayed K⁺ entry into the blood) was responsible for the lack of a significant rise in plasma [K⁺] with the IG K⁺ infusion during a meal. Nonetheless, a slow K⁺ absorption alone cannot explain the lower plasma [K⁺] profile throughout the experiment (or three- to fourfold decreases in ΔAUCK). In theory, ΔAUCK would be determined as the amount of K⁺ that appeared in the blood (or absorbed from the gut) divided by K⁺ clearance (when K⁺ clearance is reasonably constant). Therefore, ΔAUCK would be reduced if K⁺ clearance increases, and/or if plasma K⁺ appearance is reduced. We determined the degree of absorption of K⁺ that enters the stomach with a meal within our experimental time frame, and our results indicate that nearly all (~85%) of the dietary K⁺ was absorbed during the 2-h refeeding and the subsequent 3-h follow-up periods (Table 1). These data suggest that a slow K⁺ absorption cannot explain the three- to fourfold decreases in ΔAUCK with IG K⁺ infusion during a meal, and, if so, this must be due to increased plasma K⁺ clearance.

Our data indicate that the rise in plasma [K⁺] during K⁺ infusion was reduced during a K⁺-deficient meal, compared with the fasting state, regardless of route of infusion, indicating increased clearance of the K⁺ infused. This was likely due, at least in part, to increased insulin levels during a meal, which stimulate cellular K⁺ uptake (1, 12). However, insulin’s effect alone cannot entirely account for the lack of a significant rise in plasma [K⁺] with the IG K⁺ infusion during a meal, as plasma [K⁺] increased significantly with the systemic or intraportal infusion during a meal. Therefore, there must be an additional factor that accounts for enhanced clearance of plasma K⁺ with the IG K⁺ infusion during a meal. Despite the lack of increase in plasma [K⁺], there was a significant increase in renal K⁺ excretion with IG K⁺ infusion during a meal. Although absolute amounts of renal K⁺ excretion showed a tendency to be lower, renal efficiency, defined as the ratio of increase in renal K⁺ excretion to plasma [K⁺] (i.e., ΔU/K/ΔAUCk), was markedly enhanced with the IG infusion during a meal compared with other routes of infusion (Fig. 6C). On the other hand, the apparent reduction in absolute amounts of renal K⁺ excretion suggests that extrarenal cellular K⁺ uptake was increased with IG K⁺ infusion during a meal. Since this occurred without a significant increase in plasma [K⁺], it is likely that the efficiency of cellular K⁺ uptake was also enhanced. This effect may be more dramatic than the effect on K⁺ excretion, explaining that absolute amount of K⁺ excretion was less with IG K⁺ infusion during a meal, compared with other infusions, even with enhancement of renal efficiency. Thus our data suggest that the lack of a significant rise in plasma [K⁺] with the IG K⁺ infusion during a meal is due to enhanced efficiency of both renal and extrarenal K⁺ handling.

Efficiency of renal K⁺ excretion was markedly enhanced only when the IG K⁺ infusion was combined with a meal (Fig. 6C). In other words, K⁺ excretion efficiency was enhanced when K⁺ entered the stomach, together with a meal, as in the normal situation of dietary K⁺ intake. Thus there may be a mechanism in the gut for sensing of normal dietary K⁺ intake (i.e., the presence of both a meal and K⁺), which provokes enhanced renal K⁺ excretion efficiency. Such a mechanism may be important for ensuring that renal K⁺ excretion is increased only when a meal includes K⁺ (which increases total body K⁺ content), but not when a meal lacks K⁺, and not when plasma [K⁺] transiently increases as a result of a K⁺ shift between intracellular and extracellular spaces (without increases in total body K⁺ content), such as in exercise.

What is the mechanism by which the presence of both meal and K⁺ are sensed in the stomach (or the gut)? One possibility is that there is a type of cells in the stomach or the gut that senses K⁺, but this sensing requires the presence of nutrients (e.g., glucose) from a meal. Alternatively, K⁺ may be sensed in the intestine rather than the stomach, and this K⁺ sensing is affected by a meal as follows: without a meal (i.e., with empty stomach), the K⁺ infused into the stomach may be rapidly absorbed there before it can reach the intestine. K⁺ was infused in our preliminary study as 300 mM KCl solution at a volume rate of 40 μl/min. As the KCl solution was slowly dripped onto the surface of the stomach, a high K⁺ gradient from the lumen to the stomach cells might allow a rapid K⁺ absorption in the stomach. However, with a meal, the K⁺ infused into the stomach may be mixed and retained by food, carried over to the intestine, and sensed by K⁺-sensing cells there. Regarding this possibility, it would be important to test whether a direct K⁺ infusion into the intestine stimulates renal K⁺ excretion in the absence of a meal.

One may argue that the relationship between plasma [K⁺] and K⁺ excretion may not necessarily be linear, and the apparent increase in renal efficiency of K⁺ excretion with IG infusion during a meal may be due to smaller increases in plasma [K⁺]. Regarding this, our separate study showed that systemic K⁺ infusion at a rate of 40 mg·kg⁻¹·h⁻¹ increased plasma [K⁺] by 0.67 ± 0.09 mM (n = 4) or ~50% of the increase with 100 mg·kg⁻¹·h⁻¹ in the present study, which was accompanied by increases in renal K⁺ excretion (during 2-h K⁺ infusion), equivalent to only ~15% of that with 100 mg·kg⁻¹·h⁻¹. These data indicate that renal efficiency, i.e., the ratio of increases in K⁺ excretion to plasma [K⁺], was actually lower rather than higher, with smaller increases in plasma [K⁺]. This is directly supported by studies of the relationship between plasma [K⁺] and renal K⁺ excretion in dogs (23, 24). In fact, in the present study, renal efficiency was lower during the first hour, when [K⁺] was lower, than the second hour of K⁺ infusion (data not shown) in all groups, except for the group of IG K⁺ infusion during a meal, in which renal efficiency was very high in the first hour because of a significant increase in renal K⁺ excretion in the absence of an increase in plasma [K⁺] (Fig. 5). Taken together, these data suggest that the apparent increase in renal efficiency with IG infusion during a meal cannot be accounted for by a nonlinear relationship between plasma [K⁺] and renal K⁺ excretion.

Our data clearly indicate that intraportal K⁺ infusion resulted in plasma [K⁺] and renal K⁺ excretion profiles identical to those with systemic K⁺ infusion, regardless of whether the K⁺ infusions occurred with or without a meal. These data suggest either that portal venous or hepatic K⁺ sensing does not exist or that, if it does, its impact on K⁺ homeostasis is quantitatively insignificant. Morita et al. (14) demonstrated that intraportal infusions of KCl in rats increased HANA and urinary K⁺ excretion. However, in their experiments for measurement of HANA, KCl solution was injected into the PV as a bolus. If the bolus injection was given in a very short period of time, the hepatoportal area might be exposed to very high [K⁺]. For example, if the 50 mM KCl solution was given in 3 s at the dose of 1.0 ml/kg (Fig. 2 of Ref. 14), the portal venous...
[K⁺] might rise to a level of ~28 mM above basal [assuming portal plasma flow of 36 ml·kg⁻¹·min⁻¹ in rats = 1.04 ml·min⁻¹·g liver⁻¹ (10) × 34.5 g liver/kg body wt (11)]. Although this exposure might be of a short duration, such high [K⁺] would depolarize most of cells in the area. Therefore, it is not surprising to see significant responses of HANA to portal K⁺ injection. In their experiments for measurement of urinary K⁺ excretion, 50 mM KCl were infused for 30 min at a rate of 50 µl·kg⁻¹·min⁻¹ (via the PV and the vena cava). This small rate of K⁺ infusion did not alter plasma [K⁺], but was reported to increase urinary K⁺ excretion. Therefore, there may be K⁺ sensors in the PV or liver and a kaliuretic reflex from these sensors. However, our data indicate that such a kaliuretic reflex may be quantitatively insignificant or undetectable under the present conditions of dietary K⁺ intake.

Most homeostatic regulation in the body is under feedback control, as it offers a robust control (13). However, this type of control can be slow to respond to an external disturbance and inevitably mandates an error signal, a significant disturbance of the system. In the present study, renal K⁺ excretion increased as plasma [K⁺] increased during the systemic K⁺ infusion, a renal response that certainly helps prevent excessive rises of plasma [K⁺] above basal, constituting the classic feedback mechanism. However, activation of this mechanism required substantial increases in plasma [K⁺] (i.e., ~1.3 mM in the fasting state). In contrast, feedforward control would provide a quick control of output function (e.g., renal K⁺ excretion) in anticipation of rise of the signal (i.e., plasma [K⁺]). This type of control may add speed or accuracy to the control (at the expense of robustness). Providing evidence for a gut factor that senses dietary K⁺ intake and enhances renal efficiency of K⁺ excretion, the present data support the feedforward control of K⁺ homeostasis proposed by Rabinowitz (16, 17). With this mode of control, significant increases in plasma [K⁺] were prevented during the IG K⁺ infusion. The combination of both feedback and feedforward mechanisms may provide both robustness and accuracy (or speed) of the regulation, which appears to be the case in the regulation of K⁺ homeostasis.

In summary, the present data indicate that intraportal K⁺ entry was not sensed by the body, as it resulted in plasma [K⁺] and renal excretion profiles very similar to those during systemic K⁺ infusion. In contrast, IG K⁺ infusion, when combined with a meal (K⁺ deficient), increased plasma K⁺ clearance and prevented significant increases in plasma [K⁺] during the K⁺ infusion. These data suggest that there is sensing of K⁺ intake in the gut, but not in the PV or the liver, which increases plasma K⁺ clearance (via increasing the efficiency of renal and/or extrarenal K⁺ handling), and thereby maintains [K⁺] homeostasis during dietary K⁺ intake.

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