Eur J Nutr (2006) 45:342–348
DOI 10.1007/s00394-006-0604-0

ORIGINAL CONTRIBUTION

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Organic potassium salts or fibers effects on mineral balance and digestive fermentations in rats adapted to an acidogenic diet

Received: 19 July 2005
Accepted: 10 May 2006
Published online: 8 June 2006

Abbreviation SCFA: short-chain fatty acid

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Summary *Background* Fibers and potassium (K) organic salts in plant foods are liable to affect Ca and Mg balance at digestive and renal levels, respectively. K organic salts could counteract the acidifying effects of western diets and consequences of excess NaCl. *Aim of the study* To study this question, male rats were adapted to a basal acidifying low-K (LK) diet, or to diets supplemented with a fiber mix (LK/F), or K citrate (HK) or both (HK/F). *Results* HK and HK/F diets displayed a marked alkalinizing effect in urine and promoted citraturia, but this effect was not modulated by fibers. The effect of fibers on Ca digestive absorption was more potent than K citrate effect on Ca renal excretion. In contrast, K citrate effect on kidney Mg excretion was more effective than that of fibers on Mg digestive absorption, a maximal effect on Mg balance was observed in rats fed the HK/F diet. Digestive fermentations in rats fed the LK/F diet were characterized by high-propionic acid fermentations and succinate accumulation. In rats adapted to the HK/F diet, K citrate supplementation depressed succinate and increased butyrate concentrations. *Conclusion* Organic anions arising from digestive fermentations seem to be not directly involved in the alkalinizing effects of plant foods. Fibers and organic K salts exert distinct effects on Ca and Mg metabolism, but with interesting interactions as to Mg balance, digestive fermentations and urine pH.

Keywords fibers – organic anions – potassium – fermentation – acid–base balance – magnesium – calcium – rat

Introduction

Fruits and vegetables are a major source of micronutrients such as antioxidants (vitamin C, carotenoids, polyphenols) as well as of minerals, and their health effects are nowadays consistently taken into account in the prevention of chronic diseases such as cardiovascular diseases or diabetes [1–3]. Besides, there is an increasing awareness of the interest of these plant foods in less explored domains: for example their role as major source of K, together with Mg, under the form of alkalinizing salts (chiefly citrate and malate), with a potential to prevent some chronic pathologies such as hypertension, osteoporosis or osteopenia [4–6]. Plant foods are also a source of fibers which contribute to their health benefits, primarily through the production of short chain fatty anions (SCFA) in the large intestine by microbial symbiotic fermentations [7]. The daily intake of unavailable carbohydrates in western countries (15–20 g/d), together with endogenous sources (sloughed epithelial cells, digestive secretions), result

in a total substrate supply of about 30 g/d for colonic fermentations. As the yield of the colonic fermentations for SCFA production is roughly 50%, this process should generate around 15 g SCFA/d, which are readily absorbed through the colonic mucosa [7]. SCFA in the large intestine appear thus as a major source of organic anions of digestive origin and other organic anions (succinate, lactate and galacturonate) are seldom found in the colon in significant amounts [8, 9].

The fermentation of the nondigestible carbohydrates may influence the intestinal absorption of minerals, especially calcium (Ca) and magnesium (Mg) [10, 11]. SCFA production is accompanied by a lowering of the cecal content pH, which increases mineral solubility and potentially improves mineral absorption [12]. SCFA might also directly influence mineral absorption by forming complexes with divalent cations, leading to an increased uptake by intestinal cells [13]. Mechanisms of SCFA absorption in the large intestine are complex [14] and some of them involve a parallel absorption of cations (K^+ and/or Na^+) and might have alkalinizing consequences [15].

To further address this question, groups of rats were adapted to 'westernized' acidogenic diets (using diets relatively high in protein and NaCl, and poor of alkanizing anions), which were supplemented with fibers (a inulin/pectin mix), or an alkalinizing K salt (K citrate) or both. The effects of these diets were examined on (i) digestive fermentations in the large intestine, (ii) urine acidification or alkalinization and (iii) apparent balances of K, Mg and Ca.

Materials and methods

Experimental diets

Four experimental diets were used namely a low K diet (LK diet), a low K/fibers diet (LK/F diet), a high K diet (HK diet) and a high K/fibers diet (HK/F diet). All the diets contained (in g/kg) casein 200 (Louis François CIE, Saint-Maur, France), methionine 3, fat 100 (maize oil), cholesterol 2.5, sucrose 100, cellulose 25, NaCl 15, $CaH(PO_4)$ $2(H_2O)$ 12.8, $MgSO_4(7H_2O)$ 5, KCl 4.8 (above ingredients from Sigma, St. Louis, MO), together with trace element mix 10 and vitamin mix 10 each (AIN-93; Bethlehem, PA, USA) and wheat starch *quantum satis* for 1000 g (here 467 g/kg in average). Fiber diets were prepared on the same basis as the control diet, by adding pectin and inulin (25 g/kg each), at the expense of wheat starch. High K diets were also prepared on the same basis as the control diet, by adding 40 g/kg K_3 citrate (H_2O), at the expense of wheat starch. The final concentrations of Na, Ca and Mg in all diets were 5.9, 3.0 and 0.5 g/kg, respectively. Dietary K concentration was either 2.5 (low K diets) or 15.1 g/kg (high K diets).

Animals and sampling procedures

Rats were maintained and handled according to the recommendations of the INRA Ethics Committee, in accordance with decree No. 87–848. Male Wistar rats (IFFA/CREDO, L'Arbresle, France) weighing approximately 180 g were randomly allocated to four groups of 8 rats and fed for 21 days with one of the four semi-purified diets distributed as a moistened powder. The rats were housed in Nalgene metabolic cages (UAR, Villemoisson, 93360 Epinay/Orge) with feeder chamber outside the cage, minimizing food spillage. The separator device allows fecal pellets to roll downside of a stainless steel funnel (itself directing urine to collector vessel) to be collected in tubes. Animals were maintained in temperature-controlled conditions (22°C) with a dark period from 2000 h to 0800 h and access to food during the dark period and free access to water (distilled water). Body weight was recorded on days 0, 7, 14, 21 of the experiment; food intake determination and collection of urine were performed on 4 consecutive days at the end of the experiment.

At the time of sampling (0900 h), rats were anesthesized with sodium pentobarbital (40 mg/kg) and maintained on a plate at 37°C. Blood was drawn from the abdominal aorta into an heparinized syringe and plasma was obtained after centrifugation at 10,000×*g* for 2 min. The cecum was removed, weighted and the content collected in microfuge tubes. Plasmas, urines and cecal contents were stored at −20°C until analysis. Later, the rats were killed by an overdose of pentobarbital.

Analytical procedures

Glucose, lactate, ammonia, urea were measured by enzymatic procedures as previously described as well as glutamine and 2-ketoglutarate (2-KG) [16]. Enzymes and coenzymes were purchased from Sigma (St Louis, MO). Fecal materials were submitted to dry-ashing (10 h at 500°C). The resulting ash was redissolved in HCl (6 mol/l) and made up to an appropriate volume with lanthanum solution (1 g/l). Na^+ and K^+ in plasma and urine were quantified by flame photometry (PH90/ISA, Pouilly, France). Ca^{2+} and Mg^{2+} were quantified by PE560 atomic absorption spectrometer (Perkin Elmer, St-Quentin-en-Yvelines, France).

For analysis of anions, biological samples were diluted with milli-Q water (cecal supernatants 200-fold and urines 400-fold) and analyzed using a DX320 Dionex chromatograph (Dionex; Sunnyvale, CA) [17].

Table 1 Daily food intake, gain weight, urinary and cecal parameters (Mean values with their standard errors for eight rats per group)

	LK diet		LK/F diet		HK diet		HK/F diet		ANOVA (*P value*)		
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Fiber (F)	Potassium (K)	F × K
Food intake, g/d	17.45	± 0.53	17.88	± 0.52	17.91	± 0.46	18.33	± 0.55	NS	NS	NS
Weight gain, g/d	6.32	± 0.36	6.29	± 0.29	5.78	± 0.24	5.93	± 0.12	NS	0.084	NS
Urine excretion, ml/d	17.54	± 1.48	16.69	± 2.56	17.81	± 1.02	18.63	± 1.55	NS	NS	NS
Urine pH	5.70	± 0.02	5.71	± 0.02	7.18	± 0.11[a]	7.38	± 0.08[bc]	NS	<0.001	NS
Caecum total weight, g	2.41	± 0.18	3.99	± 0.31[a]	2.74	± 0.24	4.39	± 0.26[b]	<0.001	0.087	NS
Caecum pH	7.50	± 0.00	5.50	± 0.00[a]	7.63	± 0.13	5.88	± 0.24[b]	0.001	0.065	NS
Stool dry weight, g	4.79	± 0.39	7.79	± 0.46[a]	5.14	± 0.16	7.98	± 0.37[b]	<0.001	NS	NS

[a]Significant different between LK diet and LK/F diet, or HK diet ($P < 0.05$)
[b]Significant different between HK diet and HK/F diet ($P < 0.05$)
[c]Significant different between LK/F diet and HK/F diet ($P < 0.05$)

SCFA were measured by gas–liquid chromatography on cecal supernatants (40,000×*g*, 15 min) [18].

Statistical analysis

Values are given as the means ± SEM and significance of differences ($P < 0.05$) between mean values was determined by two-way analysis of variance (ANOVA) coupled with the Student's Newman–Keuls' Test.

Results

As shown in Table 1, the daily food intake and weight gain were not significantly different between the experimental groups. The cecal volume was significantly enlarged (+60 to 66%) in rats fed the fiber-containing diets, and the daily stool weight showed a parallel change. The cecal pH, around 7.5 in rats fed the fiber-free diet, was markedly acidified by the presence of fiber in the diet, down to 5.50 in the LK/F diet group. The cecal pH was significantly less acidic ($P < 0.001$) in rats adapted to the HK/F diet (pH 5.88).

Urine volume was similar in the different diet groups (around 18 ml/24 h). Urine pH was definitely acidic (near 5.7) in rats adapted to the LK diets, whereas urine pH was significantly higher (slightly alkaline) in rats fed the HK diets, especially the HK/F diet. Arterial blood pH and bicarbonate concentration were not significantly altered by the diet conditions (data not presented).

Figure 1 shows that, compared to fiber-free conditions, there was a substantial increase of the cecal SCFA pool in rats fed the fiber diets, which exhibited high-propionic acid fermentations. It is noteworthy that butyrate was very low in rats fed the LK/F diet, in acidic

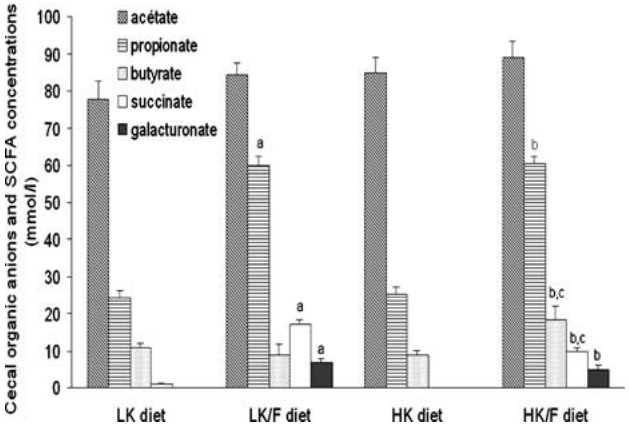

Fig. 1 SCFA and organic anions cecal pool in rats adapted to a control acidogenic diet supplemented with fiber or K citrate, or both. Data are means (in µmol/cecum) ± SEM for 8 rats in each group, urines being collected over 4 consecutive days before rat slaughter and pooled. [a]Significant different between LK diet and LK/F diet, or HK diet ($P < 0.05$). [b]Significant different between HK diet and HK/F diet ($P < 0.05$). [c]Significant different between LK/F diet and HK/F diet ($P < 0.05$)

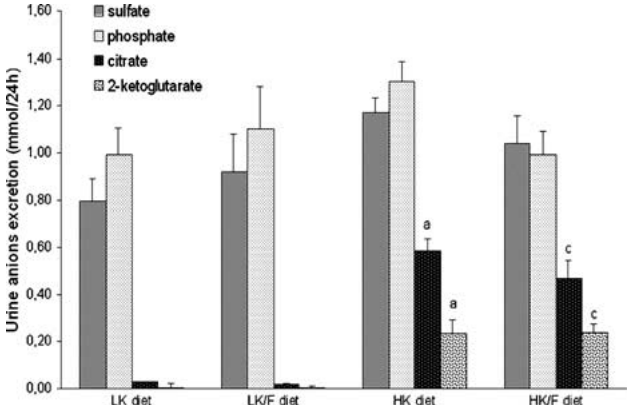

Fig. 2 Urine anions excretion in rats adapted to a control acidogenic diet supplemented with fiber or K citrate, or both. Data are means (in µmol/24 h) ± SEM for 8 rats in each group, urines being collected over 4 consecutive days before rat slaughter and pooled. [a]Significant different between LK diet and LK/F diet, or HK diet ($P < 0.05$). [b]Significant different between HK diet and HK/F diet ($P < 0.05$). [c]Significant different between LK/F diet and HK/F diet ($P < 0.05$)

pH conditions, whereas butyrate was present in much greater amounts in the cecum of rats fed the HK/F diet, in less acidic pH conditions (98 μmol/cecum vs. 26 μmol/cecum in rats fed the LK diet). In rats fed the LK/F diet, large quantities of succinate (around 70 μmol/cecum) were found in the cecum together with noticeable amounts of galacturonate (27 μmol/cecum). In rats adapted to the HK/F diet, the accumulation of succinate and galacturonate was lesser and small amounts of citrate were detected (0.61 μmol/cecum).

Figure 2 shows that urine excretion of inorganic anions (SO_4 and PO_4) was not significantly altered by the diet conditions. Citrate and 2-KG excretion was nearly undetectable in rats fed the low K diets whilst excretion rate of these anions was substantial in rats fed the high K diets, with practically no influence of fibers. Chloride excretion was high (around 6 mmol/d) but not affected by the diets conditions.

Urine was the major route of K excretion in all diet conditions and grossly reflected dietary intake. The fecal K excretion was extremely low with the LK (control) diet (12 μmol/d, around 2% of total excretion), it was strongly enhanced by fibers in rats adapted to the LK/F diet (115 μmol/d, 15% of total excretion). In rats fed the HK diets, the fecal excretion still represented a minor part of total K excretion (2% with the HK diet and 4% with the HK/F diet) (data not presented). Dietary fibers slightly enhanced the digestive absorption of Ca and Mg in rats adapted to the LK diets, whilst this fiber effect was less pronounced in high K conditions (Table 2).

Ca excretion in urine was not affected by dietary fibers but was markedly reduced when K citrate was present in the diet. Ca excreted in urine represented a minor part of absorbed Ca, namely around 5% in rats fed the low K diets and 2% in those fed the high K diets. As a whole, Ca retained in the body was significantly enhanced only in rats fed the fiber diets. Urine Mg excretion was markedly enhanced by fiber in rats adapted to the low K level, on the opposite it was strongly reduced in rats adapted to the HK/F diet. Mg excreted in urine represented a major part of absorbed Mg in rats adapted to the low K level (around 84%), this percentage was markedly reduced in rats adapted to the high K level especially in those fed the HK/F diet (27%). Rats fed the low K diets retained a small percentage of ingested Mg (9–13%) whereas those adapted to the high K level exhibited a much greater retention, particularly with the HK/F diet (48%) (data not presented).

Discussion

Dietary fibers had a marked acidifying effect on the cecal pH, chiefly via SCFAS production, as previously reported [7, 19, 20]. It appears that active fermentations in the large intestine had a limited effect on blood or urine pH, in low-K diets conditions to the less, whereas there was a small but significant fostering of the alkalinizing effect of K citrate in urine by fibers in high-K conditions (HK/F diet). The dietary K level markedly affected K excretion in the feces (together with the presence of fibers) whereas cecal K concentrations were not altered by the diet conditions (in the range of 9–12 μmol/g). It has been calculated that SCFA anions production in the large intestine is frequently greater than organic anions intake from the diet [21]. Some processes implicated in SCFA

Table 2 Magnesium and calcium parameters (Mean values with their standard errors for eight rats per group)

	LK diet		LK/F diet		HK diet		HK / F diet	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Calcium								
Intake, μmol/d	1.31	± 0.04	1.33	± 0.04	1.34	± 0.05	1.39	± 0.04
Fecal excretion, μmol/d	0.59	± 0.02	0.42	± 003[a]	0.58	± 0.04	0.54	± 0.03[c]
Urine excretion, μmol/d	0.04	± 0.01	0.04	± 0.01	0.01	± 0.00[a]	0.02	± 0.00[c]
Absorption (% intake)	54.7		68.6		56.7		60.6	
Urine excretion (% absorbed)	5.9		4.4		1.3		2.0	
Magnesium								
Intake, μmol/d	0.35	± 0.01	0.36	± 0.01	0.37	± 0.04	0.35	± 0.01
Fecal excretion, μmol/d	0.17	± 0.01	0.12	± 0.00[a]	0.16	± 0.01	0.12	± 0.01[b]
Urine excretion, μmol/d	0.16	± 0.02	0.21	± 0.02[a]	0.13	± 0.03	0.07	± 0.01[bc]
Absorption (% intake)	52.8		67.6		56.7		68.4	
Urine excretion (% absorbed)	84.2		84.0		35.0		26.9	

The absorption was calculated according to the following equation: 100 * (mineral intake − fecal mineral excretion)/(mineral intake)
The urinary excretion was calculated according to the following equation: 100 * (urinary mineral excretion)/(mineral intake − fecal mineral excretion)
[a]Significant different between LK diet and LK/F diet, or HK diet ($P < 0.05$)
[b]Significant different between HK diet and HK/F diet ($P < 0.05$)
[c]Significant different between LK/F diet and HK/F diet ($P < 0.05$)

absorption involve an exchange between a $SCFA^-$ anion and a bicarbonate ion (HCO_3^-), transferred from the extracellular body fluids into the colonic lumen [13, 22]. More specifically, butyrate (highest in rats fed the HK/F diet) is a major energetic fuel for the colonic mucosa and has been shown to be metabolized in priority, compared to other substrates such as glucose or glutamine [23]: this glutamine-sparing effect could be relevant in terms of acid–base control since glutamine is an effective precursor of neutralising metabolites (HCO_3^- and NH_3) in kidneys [24].

The present data indicate that there could be some interactions between fiber fermentation and dietary K citrate. The presence of unabsorbed anion in the cecum is expectable with poorly absorbed molecules such as galacturonate, oxalate or tartarate but citrate is generally considered as well absorbed and its metabolism by the microflora is poorly known. Citrate is considered as being rapidly absorbed in the small intestine, through a Na-dependent process [25] but little is known about the rate of citrate absorption when present in the high K/Na ratio of conditions characteristics of the HK/F diet, as well as to the influence of viscous fibers such as pectin. With the present fiber mix (inulin/pectin/cellulose), acidic fermentations, down to pH 5.5 in LK conditions, favored high-propionic acid fermentations, together with a marked accumulation of succinate (a major precursor of propionic acid metabolism) and of some galacturonate (probably arising from pectin breakdown). The presence of K citrate in the HK/F diet elicited substantial alterations of the cecal fermentations: less acidic luminal pH, lowering of succinate and phosphate concentrations and a marked rise of butyrate concentration. The mechanisms of this effect of K citrate are still uncertain but this situation is reminiscent of previous investigations using apple extracts (rich in K malate together with polyphenols) [9]. In low-K conditions, K in the large intestine lumen could essentially represent intracellular bacterial K [26] and it is conceivable that a competition could take place between bacterial K needs and effective K reabsorption through the mucosa, with possible consequences on bacterial metabolism and SCFA profile in the digestive contents.

The present experiment also indicates that, in low-K conditions (corresponding to around 1 g/d potassium in humans), Mg could make a significant contribution to counteract acid excretion by kidneys since its excretion rate was in the 0.16–0.20 μmol/d range (corresponding theoretically to 0.36 positive μEq/d) compared to 0.81–0.89 μmol/d for K. This Mg contribution was probably limited by the fact that the present diets contained a moderate level of Mg (0.5 g/kg) but this is consistent with the fact that low-K foods are, in general, also poor in Mg. It must be noted that K and Mg were not sufficient to counteract urine acidification (especially by sulfate ions), even if the induction of glutaminolysis in kidneys should also supply ammonium ions [27]. When the dietary K supply is affluent (high K diets), the quantities of $KHCO_3$ arising from K citrate metabolization are effective to raise urine pH up to 7.0–7.4 and in this case the contribution of the divalent cations (Mg, Ca) to urine neutralization is probably negligible, all the more since their urinary flux was markedly depressed.

The present data confirms that soluble fibers, especially fructanes, are very effective to enhance Ca absorption as previously shown [28, 29] but it must be noted that the fiber effect on Ca absorption was greater in low K conditions (+27%) than in high K conditions (+14%). On the other hand, K citrate led to a significant reduction in renal Ca excretion (in absolute value as well as in percentage of absorbed Ca), but this effect on Ca balance was relatively minor compared to that of fibers. Total Ca excretion was lesser in rats fed the LK/F diet than in those fed the HK/F diet, in spite of a reduced urine Ca excretion in the latter. This could reflect the less acidic pH conditions observed in the large intestine of rats fed the HK/F diet (5.88), compared to those fed the LK/F diet (5.49), leading to a lesser absorption rate in the large intestine. Nevertheless, the overall Ca retention in rats fed the HK/F diet was still in same range as in rats fed the HK diet, and substantially greater than in LK controls.

For Mg, the effect of fibers was also prevailing over that of K citrate for intestinal absorption, fiber effects being essentially exerted at the large intestine level [29]. In contrast to Ca, a minor part of Mg was retained in the body in basal conditions (less than 10% vs. 50–60% for Ca). However, due to marked changes in urine Mg excretion under the influence of K citrate, Mg retention in rats fed the K citrate diet (0.08 μmol/24 h) was greater than in rats adapted to low-K diets (0.03–0.05 μmol/24 h). In addition, there were additive effects of K citrate and fibers in the HK/F diet group (0.17 μmol/24 h). As a result, in these last group, the retention percentage of Mg (48%) was not very far from that of Ca (59%). This reflects a more effective absorption of Mg than of Ca from intestine and suggests that Mg could make a significant contribution to fixed acidity neutralization in urine with low K diets, whereas high K diets tend to spare Mg (together with Ca) [30, 31]. This sparing effect was not exerted at the expense of urine alkalinizing effect, which was similar in rats adapted to the two high K diets. K depletion is always accompanied by an increased intracellular acidity both in humans and animal models, and renal acidosis results in hypocitraturia [32]. In this view, both high K diets

were very effective in promoting citraturia, a reflect of acidosis correction at the level of citrate metabolising enzymes and citrate transport in kidneys [33, 34] but fibers did not significantly affect this process.

In conclusion, the present study suggests that organic anions salts of K, together with Mg in plant foods, play a major role in the control of urine acidification elicited by 'westernized' diets, compared to organic anions generated after fiber fermentations in the large intestine. Nevertheless, some interesting interactions between fermentable fibers and K organic anions can be distinguished: (i) additive (and/or synergistic) effects on Mg global retention, and (ii) slightly negative interaction on global Ca retention, when both categories of nutriments were simultaneously present in the diet. This effect on Ca retention in rats should be qualified for humans, which excrete a larger percentage of Ca in urine [35] and are potentially more liable to respond to alkalinizing agents.

It must be kept in mind that the present rat model, characterized by a rapid growth rate and divalent cation fixation, is more representative of the situation prevailing in adolescent/young adult than in elderlies. It is widely accepted that insuring the highest peak value of bone Ca in young adults is a promising mean of preventing osteoporosis decades later, and fruits and vegetables (rich in fiber and K organic salts) are beginning to be identified as effective factors in this respect [36].

Acknowledgement Supported by a grant from the «Agence Pour la Recherche et l'Information en Fruits et Légumes frais» (APRIFEL, Paris, France).

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