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Metabolism Clinical and Experimental 54 (2005) 1243–1249

Metabolism
Clinical and Experimental

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Effects of chronic chromium picolinate treatment in uninephrectomized rat

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Received 19 October 2004; accepted 19 April 2005

Abstract

Chromium picolinate [Cr(pic)3] is a nutritional supplement that is advocated as an adjuvant therapy for impaired glucose tolerance/type 2 diabetes because it improves glucose homeostasis. Because renal dysfunction is a major complication of type 2 diabetes, the potential impact of Cr(pic)3 on kidney function requires due consideration. This investigation takes added importance because the kidney is not only the principal route of elimination for chromium but also an organ that preferentially accumulates it. To avoid the confounding influence of chronic hyperglycemia, and its associated complications, we used the unilaterally nephrectomized (UNX) rat that shows impaired kidney function with age. We tested the hypothesis that chronic treatment of the UNX rat with Cr(pic)3 exacerbates the age-related decline in renal function. Accordingly, UNX rats were fed a diet lacking (eg, control; n = 5) or containing 5 mg/kg of Cr(pic)3 (n = 7) for 60 days. The treatment did not affect glucose tolerance as reflected by lack of any effect on changes in blood glucose concentration during glucose tolerance testing. Although nonfasting blood glucose concentrations were similar between the 2 groups, plasma insulin concentration was lower in the Cr(pic)3-treated group ($P < .05$), suggesting improved insulin sensitivity. Body weight, blood pressure, heart rate, daily food and fluid consumption, daily urinary fluid and electrolyte excretions, urine osmolality, and daily protein excretion were similar between the 2 groups before and during Cr(pic)3 treatment. Although renal excretory responses to acute administration of a 5% isotonic saline volume load were similar between the 2 groups, the Cr(pic)3-treated group displayed a more robust ability to excrete a 10% isotonic saline volume load, an effect primarily related to reduced tubular reabsorption of the filtered fluid and sodium loads. In conclusion, chronic Cr(pic)3 did not adversely affect renal function. Rather, the treatment improved the ability of the animal to dispose of an acute isotonic saline volume load, suggesting preservation of renal function in the UNX rat.

1. Introduction

The manufacture and sale of nutritional supplements is a multibillion dollar industry with various formulations of trivalent chromium contributing significantly to this market [1]. The interest in chromium supplementation stems from earlier animal studies that indicated an essential role for trivalent chromium in carbohydrate metabolism [2-4]. Subsequent observations that patients on total parenteral nutrition also develop a deficit in carbohydrate metabolism, which can be alleviated with trivalent chromium, established the essential role of trivalent chromium in human diet as well [5-8]. Because dietary chromium is poorly absorbed (about 0.5%-2%), there has been a surge of interest in use of bioavailable formulations of trivalent chromium (eg, chromium picolinate [Cr(pic)3]; ~5% bioavailable) as adjunctive therapy for impaired glucose tolerance/ type 2 diabetes [9-11]. Indeed, Cr(pic)3 ranked second in sales, after calcium supplements, with a market value of over half a billion dollar in the year 2000 [1]. Thus, chromium is the second leading inorganic element sold in the market place.

Clearly, rational and effective therapeutic strategy should minimize potential adverse effects while enhancing therapeutic efficacy of any drug or nutritional supplement. With regards to Cr(pic)3, several anecdotal case reports of individual subjects suggest renal dysfunction may be a common side effect of this nutritional supplement although a cause-and-effect relationship has not been established [10,12-15]. Awareness of the potential for adverse effects has increased after the demonstration of a clastogenic (ie, chromosomal breakage) effect of Cr(pic)3 in vitro [16-18].

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0026-0495/$ – see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2005.04.011

However, to our knowledge, adverse renal effects of Cr(pic)3 have not been verified in placebo-controlled studies using human subjects. Indeed, it has been suggested that the clastogenic potential may not be a major threat in vivo because the majority of Cr(pic)3 is distributed into the cytosol rather than the nucleus or the mitochondria [9,19]. On the other hand, the assertion that trivalent chromium supplementation is safe and effective has primarily relied on results of studies which have used normal animals without coexistence of renal dysfunction [10,11,20]. More importantly, these studies have rarely focused on the chronic renal functional effects of Cr(pic)3. Because the kidney is the principal route of elimination for Cr(pic)3 and an organ in which it accumulates [9,10,19,21], the investigation of the impact of Cr(pic)3 on a dysfunctional kidney, independent of chronic hyperglycemia and its associated complications, is warranted.

We have previously shown that removal of one kidney at 4 weeks of age leads to impaired renal function, causing a significant reduction in the ability of the animal to dispose of a saline volume load as the animal reaches 6 months of age [22,23]. It is noteworthy that renal adaptation to loss of one kidney is dependent on the age of the animal at the time of unilateral nephrectomy (UNX; [24]). In other ongoing studies, we have observed a more marked, and accelerated, deterioration of renal function in rats that have undergone UNX at about 10, rather than 4 [22,23], weeks of age. Thus, we examined the chronic impact of Cr(pic)3 on renal function of rats in whom the right kidney was removed at 10 weeks of age. Accordingly, we tested the hypothesis that chronic treatment of the UNX rat with Cr(pic)3 exacerbates the age-related decline in renal function.

2. Materials and methods

Male Wistar-Kyoto rats (9-week-old) were obtained from Harlan Laboratories (Indianapolis, Ind). All rats were maintained at constant humidity (60% ± 5%), temperature (24°C ± 1°C), and light cycle (06:00 AM to 06:00 PM). Unless otherwise indicated, animals had free access to food and water.

One week after arrival, the right kidney was removed from each rat under pentobarbital anesthesia (50-60 mg/kg, IP) and postoperative analgesia (1 mg/kg butorphanol, SC) [22,23,25]. After 2 weeks to allow for compensatory renal hypertrophy, the animals were subdivided and either remained on the standard rat diet (Harlan Teklad diet no. 8604; n = 5) or were switched to the standard diet that was supplemented with 5 mg/kg of Cr(pic)3 (Harlan Teklad diet no. 03326; n = 7); the diet contained 5 mg of Cr(pic)3 rather than 5 mg/kg of Cr as Cr(pic)3. It is noteworthy that others have used diets containing more than 100 mg/kg of Cr(pic)3 [20]. We used the 5 mg/kg of Cr(pic)3 diet because, based on measured daily intake of ~20 g food, this diet provides Cr(pic)3 to the animal in doses that are closer to those consumed by human subjects [9]. Hemodynamic parameters (tail cuff; IITC/Life Science Instruments, Woodland Hills, Calif) and daily metabolic data were collected before as well as 14, 28, and 60 days after initiation of Cr(pic)3 treatment. For daily metabolic data, the animals were housed individually in metabolic cages. After a period of 3 days of acclimation, 2 consecutive 24-hour urine samples were collected and daily consumption of food and fluid measured. Each rat underwent a glucose tolerance test at about 8 weeks after initiation of dietary Cr(pic)3 supplementation and before renal function studies. For glucose tolerance testing, after an overnight fast, each rat was injected with a glucose load (2 g/kg, IP). Blood samples were obtained after a 1- to 2-mm cut at the end of the tail; a drop of blood sample was placed directly on a test strip and glucose concentration measured with a glucometer [23,25]. Nonfasting blood samples were collected for determination of blood glucose concentration and plasma insulin concentrations by radioimmunoassay (ICN Biomedicals, Costa Mesa, Calif; [26]).

For renal function studies in the conscious animal, each rat was preimplanted with femoral vessels catheters and a bladder cannula under pentobarbital anesthesia (50-60 mg/kg, IP) followed by postoperative analgesia (1 mg/kg butorphanol, SC). Two days after the surgical procedure, each rat was placed in an environmental conditioning unit to which the animal was acclimated for several hours, 5 days before renal function studies. The arterial and venous catheters were flushed with isotonic saline containing 5 U/mL of heparin.

To determine the glomerular filtration rate (GFR), each rat received an intravenous injection of 0.2 mL of isotonic saline containing a priming dose of 2 μCi of ^{3}H-inulin (Dupont Co, Boston, Mass), followed immediately by a 20 μL/min intravenous infusion of isotonic saline containing 2.5 μCi/mL of ^{3}H-inulin [22,23,25]. After a 45-minute equilibration period, which is sufficient to achieve a steady-state radioactive level in the plasma, a 30-minute urine sample was collected for determination of baseline excretory parameters. A 30-minute volume expansion (equivalent to 5% of the animal's body weight) was then initiated with isotonic saline containing ^{3}H-inulin [22,23,25]. This was followed by infusion of isotonic saline containing ^{3}H-inulin at the rate of 20 μL/min for the remainder of the experiment. Urine samples were collected at 15, 30, 60, and 90 minutes after initiation of the saline volume load. At the midpoint of each urinary collection period, 0.2 mL of arterial blood sample was collected for determination of plasma radioactivity and electrolyte composition; the blood sample was replaced with an equal volume of isotonic saline. The next day, the infusion protocol was repeated with an isotonic saline volume load which was equivalent to 10% of the animal's body weight and administered over 30 minutes. At the conclusion of renal function studies the animals killed with pentobarbital (50 mg/kg, IV); the weight of the remaining kidney was determined for each animal.

Sodium and potassium were measured by flame photometry and used to calculate sodium and potassium

excretion. Urine osmolality was measured by an osmometer, whereas urinary protein content was measured by the Comassie blue method (Sigma, St Louis, Mo). Glomerular filtration rate and fractional excretions of water and sodium were calculated using standard clearance formulas [22,23,25].

2.1. Statistics

All data were analyzed by 1-way analysis of variance. Variables that were measured sequentially were analyzed by repeated-measures analysis of variance. Duncan post hoc test was used for comparison of mean values (significance of criteria of $P < .05$). Data are reported as means ± SEM.

3. Results

Body weight was similar between the control and Cr(pic)3-treated groups before (248 ± 5 vs 237 ± 3 g) and 60 days after initiation of Cr(pic)3 treatment (356 ± 9 vs 353 ± 7 g, control and Cr(pic)3, respectively); both groups displayed similar kidney weights [2.2 ± 0.2 vs 1.8 ± 0.1 g, $P = 0.20$; control and Cr(pic)3, respectively]. Furthermore, systolic blood pressure (123 ± 9 vs 124 ± 6 mm Hg) and heart rate (367 ± 9 vs 369 ± 10 beats per minute) were similar between the 2 groups 60 days after initiation of Cr(pic)3 treatment.

Dietary Cr(pic)3 treatment did not affect either the fasting blood glucose concentration or the response to glucose tolerance testing (Fig. 1A). However, although nonfasting blood glucose concentration was similar between the 2 groups, the Cr(pic)3-treated group displayed reduced nonfasting plasma insulin concentration, suggesting improved insulin sensitivity (Fig. 1B-C).

Daily intake of food and fluid or daily excretions of urine and electrolytes, urine osmolality, and protein excretion were similar between the 2 groups before dietary assignment (data not shown). These parameters remained similar between the 2 groups 14, 28, and 60 days after dietary assignments. Table 1 summarizes metabolic data for the experimental groups 60 days after initiation of Cr(pic)3 treatment.

It is noteworthy that subtle or even marked changes in renal function may not be recognized by assessment of daily metabolic data alone. An example is the streptozotocin-treated type 1 diabetic rat, which excretes large volumes of fluid and similar amounts of sodium in comparison to its control counterpart over a 24-hour period [27]. Yet the type 1 diabetic rat is markedly impaired in its ability to dispose of a saline volume load (5%-10% of body weight), thereby indicating impairment of the volume reflex mechanism [28,29]. Therefore, at the conclusion of the daily metabolic studies (ie, 60 days after initiation of the Cr(pic)3 treatment), renal responses to an isotonic saline volume load were determined in the conscious animal with preimplanted vascular and bladder catheters.

Fig. 2A and B shows that Cr(pic)3-treated rats displayed a similar diuretic response but a mild increase in the

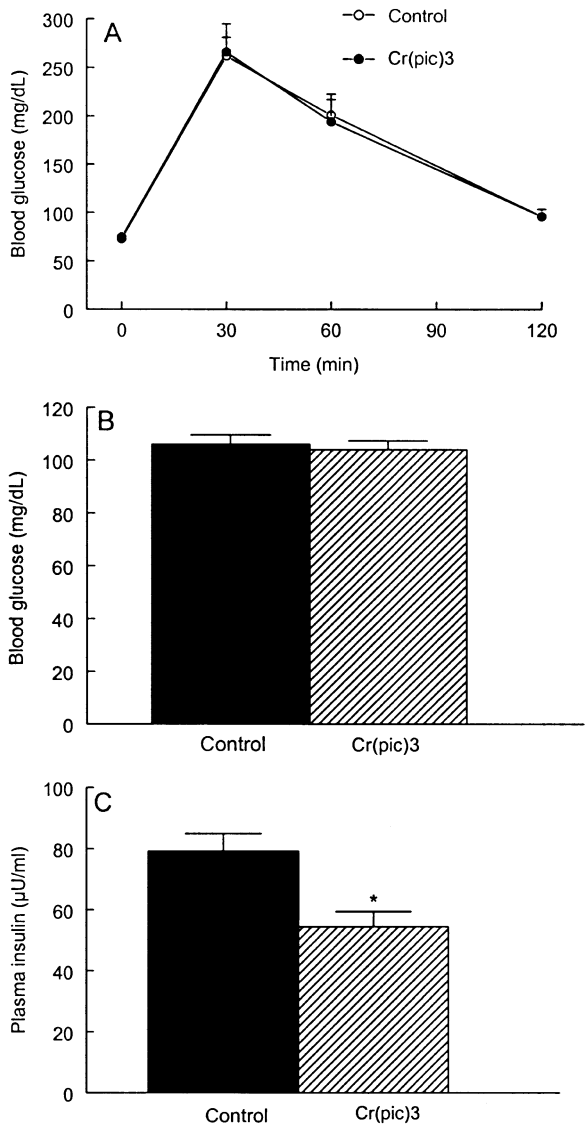

Fig. 1. Fasting blood glucose concentration (time 0) was similar between control and Cr(pic)3-treated groups and both groups displayed similar elevations in blood glucose concentration after intraperitoneal administration of a glucose load (2 g/kg). However, although nonfasting blood glucose concentration was similar between the 2 groups (B), nonfasting plasma insulin concentration (C) was lower in the Cr(pic)3-treated group. Data were collected 8 weeks after initiation of the dietary Cr(pic)3 treatment. Data are means ± SEM. *$P < .05$ compared with the control group.

natriuretic response after administration of a saline volume load (5% of body weight); these responses are lower than those of rats which undergo UNX at 4 weeks of age or sham-operated 2-kidney rats [22]. As expected, administration of a 10% saline volume load resulted in significantly greater fluid and sodium excretions in both groups compared with the 5% volume load. Interestingly, however, Cr(pic)3-treated rats displayed a more robust increase in both fluid and sodium excretions during administration of the 10% volume load (Fig. 2A-B). Potassium excretion was similar between the 2 groups during either the 5% or the 10% volume expansion (Fig. 2C).

Table 1
Daily metabolic data for the experimental groups 60 days after initiation of dietary Cr(pic)3 supplementation

Group	Food intake (g)	Fluid intake (mL)	Urine excretion (mL/d)	Na^+ excretion (mEq/d)	K^+ excretion (mEq/d)	Urine osmolality (mosM/kg)	Protein excretion (mg/d)
Control (n = 5)	20.2 ± 0.5	34.6 ± 1.0	16.3 ± 1.0	1.27 ± 0.09	5.34 ± 0.19	1746 ± 80	24.2 ± 1.3
Cr(pic)3 (n = 7)	19.3 ± 0.6	33.1 ± 1.1	15.1 ± 1.1	1.33 ± 0.07	4.87 ± 0.24	1975 ± 88	20.8 ± 1.6

Baseline GFR was similar between the 2 groups and both groups displayed similar changes in GFR during saline volume loading although the Cr(pic)3-treated group showed a numerical advantage compared with the control group (Fig. 3A). Analysis of fractional excretion and glomerular filtration data suggest that reduced tubular reabsorption of the filtered fluid and sodium loads contributes to greater diuretic and natriuretic responses to saline volume expansion during the 10% than the 5% isotonic saline volume load. Moreover, the differential in excretory responses between the Cr(pic)3-treated and the control groups during administration of the 10% volume load can be attributed to reduced tubular reabsorption of the sodium load (Fig. 3A-C).

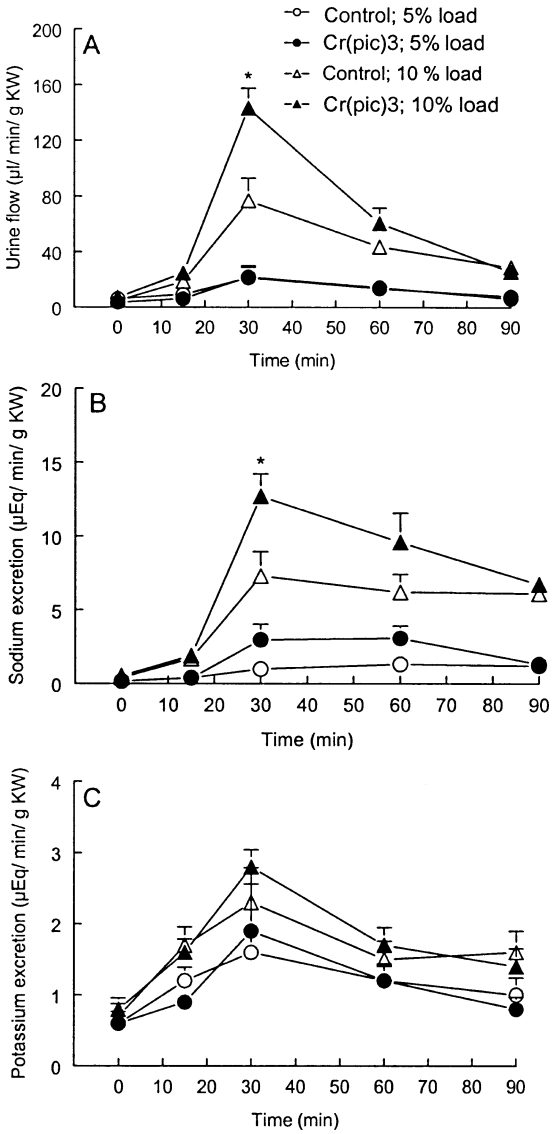

Fig. 2. Line graphs show diuretic (A), natriuretic (B), and kaluretic (C) responses of the control and Cr(pic)3-treated rats to immediate intravenous administration of an isotonic saline volume load that was equivalent to either 5% (circles) or 10% (triangles) of the animal's body weight. Data are means ± SEM. *$P < .05$ compared with other rats at the same time point.

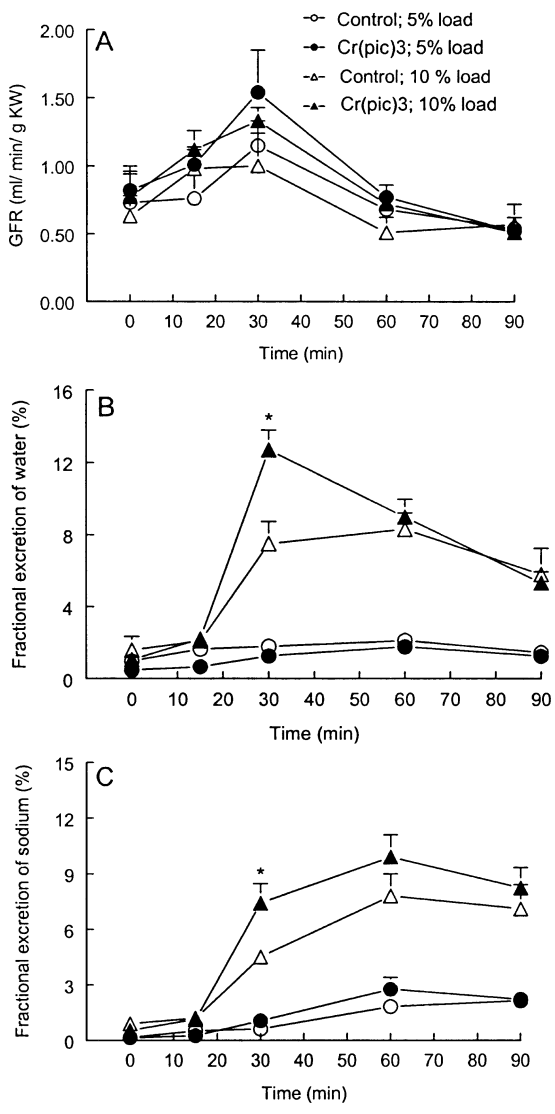

Fig. 3. Panel A shows that baseline and changes in GFR during isotonic saline loading were similar between the control and Cr(pic)3-treated rats. Panels B and C show fractional excretions of fluid and sodium, respectively, in control and Cr(pic)3-treated rats in response to either a 5% (circles) or a 10% (triangles) saline volume load. Data are means ± SEM. *$P < .05$ compared with other rats at the same time point.

4. Discussion

This study indicates that chronic treatment of rats with Cr(pic)3 does not affect blood pressure, heart rate, or the ability of the animals to thrive. Furthermore, Cr(pic)3-treated rats displayed similar nonfasting blood glucose levels but a lower nonfasting plasma insulin concentration, suggesting improved insulin sensitivity. Also of interest was the lack of any adverse effect of Cr(pic)3 on renal function. Rather, the treatment improved the ability of UNX rats to dispose of an acute saline volume load. Taken together, the data suggest that Cr(pic)3 modulates renal function independent of changes in blood glucose concentration or systemic hemodynamics.

Numerous studies have confirmed a beneficial effect of trivalent chromium [eg, Cr(pic)3] on glucose (and lipid) metabolism but the exact molecular events subserving its metabolic effects remain to be established (see Refs [10,11]). Nonetheless, several mechanisms have been reported, including increased insulin receptor binding, increased insulin receptor tyrosine kinase activity, and decreased insulin receptor tyrosine phosphatase activity. The net effect of these changes would be amplification of insulin receptor signaling culminating in improved glucose homeostasis [4,10,11,30,31]. This is consistent with the reported beneficial effect of trivalent chromium on glycemic control not only in conditions associated with insulin resistance but also in healthy subjects [10,11,32-35].

Although the beneficial metabolic effects of Cr(pic)3 have been the focus of numerous investigations, others have raised concerns regarding its safety and toxicity. Of particular concern has been the potential genotoxicity of Cr(pic)3. In 1995, Stearns et al [16] reported that Cr(pic)3 causes clastogenic damage (eg, chromosomal breakage) in Chinese hamster ovary cells. A subsequent study using cultured J774A.1 macrophage described a similar effect of the supplement [18]. Using pUC19 plasmid DNA, Speetjens and colleagues [17] showed that Cr(pic)3, in the presence of air and biologic reductant ascorbate, relaxes supercoiled DNA in a concentration-dependent manner. The authors have proposed a mechanism for this effect that involves reduction of Cr(pic)3 by ascorbate to $[Cr(II)(pic)3]^{-}$; the latter molecule is susceptible to air oxidation thereby generating hydroxyl free radicals [17]. Hydroxyl free radicals can cause severe DNA damage through any of a large and complex set of reactions ranging from oxidation of deoxyribose and base moieties to strand breaks [36].

Chromium picolinate is very stable and is able to penetrate tissues more readily compared with other forms of trivalent chromium (eg, its neutral charge and hydrophobicity). This is consistent with the observation that after long-term Cr(pic)3 supplementation in the rat, chromium is distributed into tissues although there appears to be preferential accumulation in the kidney compared with other tissues, such as the spleen and the heart [9,10,19]. Using ^{51}Cr(pic)3 injections into Sprague-Dawley rats, Hepburn and Vincent confirmed increased tissue content of Cr(pic)3 (eg, liver and kidney) and also showed preferential accumulation of ^{51}Cr in the cytosol of hepatocytes (~75%; [9]). Furthermore, these authors showed that ^{51}Cr(pic)3 is capable of entering the nucleus and the mitochondria, but these organelles showed very little accumulation of ^{51}Cr. Based on these findings, these authors suggested that the risk of damage to the DNA from generation of hydroxyl radicals is reduced because Cr(pic)3 is preferentially accumulated in the cytosol rather than the nucleus or the mitochondria [9]. Interestingly, however, in a recent publication these investigators indicate that rats given daily injection of Cr(pic)3 (38 μg) for 60 days not only excrete significant quantity of 8-hydroxy-2′-deoxyguanosine (8-OHdG) but also show increased renal tissue content of 8-OHdG [19]; 8-OHdG is a biomarker of oxidative DNA damage and repair [36,37]. Based on kinetics of uptake of ^{51}Cr(pic)3 into subcellular organelles, the authors suggest that Cr(pic)3 enters the cell intact and gets incorporated into the nucleus and the mitochondria. Nonetheless, although it is readily destroyed or removed, the brief period of exposure of these DNA-containing organelles to Cr(pic)3 is sufficient for generation of significant DNA damage [19].

It is, however, rather difficult to reconcile the potential genotoxicity of Cr(pic)3 in vivo with lack of any adverse effect on renal function in this study or with the assertion of other investigators that even high doses of chromium supplementation is safe and does not cause adverse effects [10,20]. It is plausible that residual damage from Cr(pic)3 is not sufficient to adversely affect organ function. A more likely explanation, however, could relate to the fact that ~5% of Cr(pic)3 is bioavailable after oral administration [9,10]. The animals in our study had daily intake of about 100 μg of Cr(pic)3 [based on daily intake of ~20 g of 5 mg/kg Cr(pic)3 diet]. Thus, we estimate that about 5 μg of daily intake actually reaches the systemic circulation. This contrasts with the higher levels (about 38 μg/d of Cr(pic)3) reported in the study of Hepburn and Vincent [19]. It is plausible that, similar to in vitro observations, the in vivo clastogenic effect is dose-related. The Cr(pic)3 intake of the animals in this study is several fold higher (~6-17 times), on per-kilogram basis, than those consumed by human subjects [9]. Thus, provision of diets more enriched in Cr(Pic)3 may not be applicable to the human subjects using this nutritional supplement.

In this study, we used the UNX rat to explore chronic renal effects of Cr(pic)3. The use of UNX rats was deemed appropriate in light of the following considerations. First, we have shown that removal of one kidney early in life (eg, 4 weeks of age) results in an impaired ability to dispose of a saline volume load with advancing age [22,23]. Subsequent observations indicated that renal adaptation to UNX depends on animal's age at the time of kidney removal and at the time of assessing renal responses to acute plasma volume expansion. Rats in which one kidney was removed at 10, rather than 4, weeks of age, develop a more profound

reduction in saline-induced diuresis and natriuresis compared with their sham-operated 2-kidney counterparts (Refs [22,23] and present study). In this study, the UNX rats were about 5 months of age when renal excretory responses to acute plasma volume expansion were determined. A comparison of renal fluid and sodium excretion in response to a 5% saline volume load reveals a marked reduction in the ability of the 5-month-old UNX rats vs the 6-month-old sham-operated rat to cope with acute plasma volume expansion by augmenting diuresis and natriuresis (Fig. 2; [22]). Indeed, 90 minutes after administration of the 5% saline volume load, the UNX rats in this study excreted about 10% to 15% of the administered sodium and fluid loads compared with the much larger 40% to 50% excretion by the sham-operated 6-month-old 2-kidney rats (see Refs [22,23] for sham-operated data). This deficit is related to a combination of reduced glomerular function and increased tubular reabsorption activity ([22]; Fig. 3). It is noteworthy that 6-month-old rats that had undergone UNX at 4 weeks of age display renal responses to 5% saline volume expansion intermediate between those of the 6-month-old sham-operated 2-kidney rat [22] and the 5-month-old rat that had undergone UNX at 10 weeks of age (Figs. 2 and 3). Second, given that the UNX rat develops impaired renal function with advancing age, the UNX model provides a unique opportunity to explore renal effects of Cr(pic)3 in an model of renal dysfunction lacking coexisting disorders that impact kidney function (eg, hyperglycemia). Third, progressive loss of functional renal mass is a major feature of type 2 diabetes [38], a condition for which Cr(pic)3 use is advocated.

The renal response to volume loading is complex and involves several components including (*a*) the afferent limb (ie, volume receptors, electromechanical coupling, and afferent fibers); (*b*) the central sites for neuronal processing of afferent input; and (*c*) the efferent limb (ie, release and/or action of humoral factors and renal sympathetic nerve activity; [29]). Modulation of any of these components could influence renal excretory function and thus account for the increased saline volume–induced diuresis and natriuresis in Cr(pic)3-treated rat. Nonetheless, at the level of the kidney, baseline GFR was similar between the 2 groups although Cr(pic)3-treated rats displayed generally higher, albeit nonsignificant, GFR during saline volume loading compared with the control group. Thus, reduced tubular reabsorption of the filtered fluid and sodium contributes to improved saline volume–induced diuresis and natriuresis as reflected by greater fractional excretions of fluid and sodium. Similarly, the significant increase in renal fluid and sodium excretions during administration of the 10% rather than the 5% isotonic saline load is due to reduced tubular reabsorption of the filtered load of fluid and sodium (Fig. 3A-C).

Finally, it is noteworthy that Cr(pic)3-treated rats displayed a lower ambient insulin concentration. Among its multiple and diverse effects, insulin promotes sodium reabsorption by renal tubules [39,40]. Thus, it is plausible that the improvement in saline volume–induced diuresis and natriuresis in Cr(pic)3-treated rats relate, in part, to lower plasma insulin concentration.

In conclusion, chronic treatment of the UNX rats with Cr(pic)3 does not adversely affect renal function. Rather, the treatment appears to benefit the remaining kidney. Because the UNX rat displays impaired renal function with advancing age compared with its 2-kidney counterpart [22,23], the improvement in renal function in Cr(pic)3-treated rat suggests preservation of renal function. These observations, along with a similar blood glucose concentration despite a lower plasma insulin concentration, raise the possibility that Cr(pic)3 may exert “renoprotection” in animal models of impaired glucose tolerance/type 2 diabetes that exhibit renal functional deficits. Thus, long-term studies using appropriate animal models of these disorders are needed to better establish the impact of Cr(pic)3 on the kidney.

References

[1] Mirasol F. Chromium picolinate market sees robust growth and high demand. Chem Mark Rep 2000;257:26.
[2] Mertz W, Schwarz K. Relation of glucose tolerance factor to impaired intravenous glucose tolerance in rats on stock diets. Am J Physiol 1959;196:614-8.
[3] Schroeder HA. Chromium deficiency in rats: a syndrome simulating diabetes mellitus with retarded growth. J Nutr 1966;88(4):439-45.
[4] Vincent JB. The biochemistry of chromium. J Nutr 2000;130:715-8.
[5] Jeejeebhoy KN, Chu RC, Marliss EB, et al. Chromium deficiency, glucose intolerance, and neuropathy reversed by chromium supplementation, in a patient receiving long-term total parenteral nutrition. Am J Clin Nutr 1977;30:531-8.
[6] Freund H, Atamian S, Fischer JE. Chromium deficiency during total parenteral nutrition. JAMA 1979;241:496-8.
[7] Brown RO, Forloines-Lynn S, Cross RE, et al. Chromium deficiency after long-term total parenteral nutrition. Dig Dis Sci 1986;31:661-4.
[8] Verhage AH, Cheong WK, Jeejeebhoy KN. Neurologic symptoms due to possible chromium deficiency in long-term parenteral nutrition that closely mimic metronidazole-induced syndromes. JPEN J Parenter Enteral Nutr 1996;20:123-7.
[9] Hepburn DD, Vincent JB. In vivo distribution of chromium from chromium picolinate in rats and implications for the safety of the dietary supplement. Chem Res Toxicol 2002;15(2):93-100.
[10] Lamson DW, Plaza SM. The safety and efficacy of high-dose chromium. Altern Med Rev 2002;7(3):218-35.
[11] Anderson RA. Chromium in the prevention and control of diabetes. Diabetes Metab 2000;26:22-7.
[12] Martin WR, Fuller RE. Suspected chromium picolinate–induced rhabdomyolysis. Pharmacotherapy 1998;18:860-2.
[13] Wasser WG, Feldman NS, D’Agati VD. Chronic renal failure after ingestion of over-the-counter chromium picolinate. Ann Intern Med 1997;126:410.
[14] Cerulli J, Grabe DW, Gauthier I, et al. Chromium picolinate toxicity. Ann Pharmacother 1998;32:428-31.
[15] Fowler Jr JF. Systemic contact dermatitis caused by oral chromium picolinate. Cutis 2000;65:116.
[16] Stearns DM, Wise Sr JP, Patierno SR, et al. Chromium (III) picolinate produces chromosome damage in Chinese hamster ovary cells. FASEB J 1995;9:1643-8.
[17] Speetjens JK, Collins RA, Vincent JB, et al. The nutritional supplement Chromium(III) Tris(picolinate) cleaves DNA. Chem Res Toxicol 1999;12:483-7.

[18] Bagchi M, Bagchi J, Balmoori XY, et al. Comparative induction of oxidative stress in cultured J774A.1 macrophage cells by chromium picolinate and chromium nicotinate. Res Commun Mol Pathol Pharmacol 1997;97:335-46.
[19] Hepburn DDD, Vincent JB. Tissue and subcellular distribution of chromium picolinate with time after entering the bloodstream. J Inorg Biochem 2003;94:86-93.
[20] Anderson RA, Bryden NA, Polansky MM. Lack of toxicity of chromium chloride and chromium picolinate in rats. J Am Coll Nutr 1997;16(3):273-9.
[21] Clodfelder BJ, Upchurch RG, Vincent JB. A comparison of the insulin-sensitive transport of chromium in healthy and model diabetic rats. J Inorg Biochem 2004;98:522-33.
[22] Mozaffari MS, Wyss JM. Dietary NaCl-induced hypertension in uninephrectomized Wistar Kyoto rats: role of kidney function. J Cardiovasc Pharmacol 1999;33(5):814-21.
[23] Mozaffari MS, Schaffer SW. Chronic taurine treatment ameliorates reduction in saline-induced diuresis and natriuresis. Kidney Int 2002; 61(5):1750-9.
[24] Nagata M, Scharer K, Kriz W. Glomerular damage after uninephrectomy in young rats. I. Hypertrophy and distortion of capillary architecture. Kidney Int 1992;42:136-47.
[25] Mozaffari MS, Schaffer SW. Renoprotective effects of chronic candesartan treatment in the uninephrectomized rat. J Cardiovasc Pharmacol 2003;41(1):81-8.
[26] Mozaffari MS, Roysommuti S, Wyss JM. Contribution of the sympathetic nervous system to hypertensive response to insulin excess in spontaneously hypertensive rats. J Cardiovasc Pharmacol 1996;27:539-44.
[27] Warren BK, Mozaffari MS, Patel C. Effects of inorganic fluoride on renal excretion of fluid and sodium in diabetic rats. Methods Find Exp Clin Pharmacol 1998;20(9):761-9.
[28] Patel KP, Zhang PL. Reduced renal responses to volume expansion in streptozotocin-induced diabetic rats. Am J Physiol 1989;257: R672-9.
[29] Patel KP. Volume reflex in diabetes. Cardiovasc Res 1997;34:81-90.
[30] Vincent JB. Mechanisms of chromium action: low-molecular-weight chromium-binding substance. J Am Coll Nutr 1999;18(1):6-12.
[31] Imparl-Radosevich J, Deas S, Polansky MM, et al. Regulation of phosphotyrosine tyrosine phosphatase (PTP-1) and insulin receptor kinase by fractions from cinnamon: implications for cinnamon regulation of insulin signaling. Horm Res 1998;50:177-82.
[32] Morris B, Peacey SR, MacNeil S. Enhancement in insulin sensitivity in healthy volunteers following supplementation with chromium picolinate. Med Biochem 1998;1:65-72.
[33] Anderson RA, Polansky MM, Bryden NA, et al. Supplemental-chromium effects on glucose, insulin, glucagons, and urinary chromium losses in subjects consuming controlled low-chromium diets. Am J Clin Nutr 1991;54:909-16.
[34] Cheng N, Zhu X, Shi H. Follow-up survey of people in China with type 2 diabetes mellitus consuming supplemental chromium. J Trace Elem Exp Med 1999;12:55-60.
[35] Anderson RA, Cheng N, Bryden NA, et al. Elevated intakes of supplemental chromium improve glucose and insulin variables in individuals with type 2 diabetes. Diabetes 1997;46:1786-91.
[36] Cadet J, Delatour T, Douki T, et al. Hydroxyl radicals and DNA base damage. Mutat Res 1999;424:9-21.
[37] Wu LL, Chiou CC, Chang PY, et al. Urinary 8-OHdG: a marker of oxidative stress to DNA and a risk factor for cancer, atherosclerosis and diabetics. Clin Chim Acta 2004;339:1-9.
[38] Jawa A, Kcomt J, Fonseca VA. Diabetic nephropathy and retinopathy. Med Clin North Am 2004;88:1001-36.
[39] Banday AA, Siddiqui AH, Menezes MM, Hussain T. Insulin treatment enhances AT1 receptor function in OK cells. Am J Physiol 2005; 288:F1213-9.
[40] Feraille E, Marsy S, Cheval L, Barlet-Bas C, Khadouri C, Favre H, et al. Sites of antinatriuretic action of insulin along rat nephron. Am J Physiol 1992;263:F175-9.