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Absorption, excretion and retention of ^{51}Cr from labelled Cr-(III)-picolinate in rats

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Abstract The bioavailability of chromium from Cr-picolinate ($CrPic_3$) and Cr-chloride ($CrCl_3$) was studied in rats using ^{51}Cr-labelled compounds and whole-body-counting. The intestinal absorption of Cr was twice as high from $CrPic_3$ (1.16% vs 0.55%) than from $CrCl_3$, however most of the absorbed ^{51}Cr from $CrPic_3$ was excreted into the urine within 24 h. After i.v. or i.p. injection, the whole-body retention curves fitted well to a multiexponential function, demonstrating that plasma chromium is in equilibrium with three pools. For $CrPic_3$, a large pool exists with a very rapid exchange ($T_{1/2} = <0.5$ days), suggesting that $CrPic_3$ is absorbed as intact molecule, from which the main part is directly excreted by the kidney before degradation of the chromium complex in the liver can occur. $CrCl_3$ is less well absorbed but the rapid exchange pool is much smaller, resulting in even higher Cr concentrations in tissue such as muscle and fat. However, 1–3 days after application, the relative distribution of ^{51}Cr from both compounds was similar in all tissues studied, indicating that both compounds contribute to the same storage pool. In summary, the bioavailability of $CrPic_3$ in rats is not superior compared to $CrCl_3$.

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Introduction

Chromium in its trivalent form (Cr^{3+}) is generally regarded as an essential nutrient involved in the regulation of carbohydrate, lipid, and protein metabolism via an enhancement of insulin action (Mertz 1993; Anderson 1998; Vincent 2000, 2001; Cefalu and Hu 2004; Sreejayan et al. 2008). In support of this notion four lines of evidence have been presented: (1) patients on total parenteral nutrition developed symptoms of adult-onset diabetes, which was reversed by the addition of chromium (Jeejeebhoy 1999), (2) Cr-deficient rats developed insulin resistance (Striffler et al. 1995), (3) Cr absorption in humans is inversely related to the amount of chromium given in the diet (Anderson and Kozlovsky 1985), and (4) increases in serum glucose are associated with an increase in urinary excretion of Cr (Anderson et al. 1990). Moreover, an oligopeptide, *Chromodulin*, isolated from liver tissue of different species, is believed to function as part of a unique autoamplification mechanism in insulin signalling (Davis and Vincent 1997). Nevertheless, at the moment the evidence of chromium as an essential trace element is still not definite, since various technical issues hinder the advancement in this field. For example, the low intestinal absorption

of chromium or Cr supplements and the extremely low (nM) Cr concentrations present in body fluids and tissues make it difficult to perform reliable analytical determinations against the background of ubiquitous Cr. To date, no useful indicator of Cr function, no binding protein to measure, no clear diagnostic criterion for Cr deficiency is available. The best data on chromium metabolism so far have been collected already very early following the transport and excretion of ^{51}Cr in rats (Mertz et al. 1965; Hopkins 1965; Onkelinx 1977) and, to some extent, also in humans (Doisy et al. 1971; Sargent et al.1979; Lim et al. 1983) after i.v. or i.p. application of $^{51}CrCl_3$. Since dietary chromium is poorly absorbed (about 0.5–2%), there has been keen interest in the use of more bioavailable Cr formulations. For example, picolinic acid, a natural derivative of the amino acid tryptophane, is thought to facilitate chromium absorption, because the bioavailability of $CrPic_3$ has been reported to be higher (2–5%) in rats and humans as compared to other chromium compounds (Anderson et al. 1996; DiSilvestro and Dy 2007). However, despite a widespread use of $CrPic_3$, the absorption and metabolism of $CrPic_3$ has so far been studied only by rather indirect methods (i.e. by measuring urinary Cr excretion after the application of chromium). Therefore, the aim of the present study was to measure the bioavailability of chromium from $CrPic_3$ in rats using whole-body counting, which allows for the first time a comprehensive and quantitative characterization of the absorption, excretion and retention of this chromium supplement.

Methods

^{51}Cr-compounds

A solution of $^{51}CrCl_3$ (specific activity of 31.3 GBq/mg) in 0.5 M HCl was commerically obtained from PerkinElmer Life and Analytical Sciences, Boston, USA. A total of 185 MBq ^{51}Cr-activity, delivered in a single plastic flask, was diluted with 500 µl of water.

Synthesis of ^{51}Cr(trispicolinate)

The $^{51}CrPic_3 \cdot H_2O$ was synthesized according to Evans and Pouchnick (1993). In brief, 50 µl of an aqueous solution of picolinic acid (0.114 mM) and 240 µl of the diluted $^{51}CrCl_3$-tracer solution were mixed and 50 µl of an aqueous solution of $CrCl_3$ (37 µM) were added. The mixture was then incubated at 50°C over night and subsequently centrifuged through a filter device (Ultrafree-MC, 10.000 NMWL filter unit, low binding regenerated cellulose, Millipore) at $5000 \times g$ for 20 min. The reddish crystals remaining on the filter membrane were washed three times with 50 µl of ice-cold water. For the rat experiments, saturated aqueous solutions of $^{51}CrPic_3$ (0.6 mM) were freshly prepared by adding of 400 µl of water, incubation at 50°C for 30 min, followed by centrifugation at $5{,}000 \times g$ for 20 min.

The radiochemical purity of the synthesized $^{51}CrPic_3$ was determined by reverse phase HPLC (column Nucleosil C18 5U; eluent water/methanol 1:1). The activity, found in the peak at 4.6 min retention time, accounted for 95% of the injected ^{51}Cr-activity.

Animal experiments

All experiments were approved by the local committee for animal experiments (Behörde für Soziales, Familie, Gesundheit und Verbrauch, BSG, Hamburg, Nr. 37/04). Female Wistar rats (200–300 g, Charles River Germany), fed on a standard diet in pellet form (Altromin 1328) were used for all experiments. Rats had access to tap water ad libitum.

The rats were fasted 4–6 h before and 1 h after the respective administration of labelled ^{51}Cr-compounds. Aqueous solutions were administered by gastric intubation, intraperitoneal or intravenous (tail vein) injections. After administration of the compounds, rats were kept in cages of 3–4 rats, except for experiments in which some rats were kept in individual metabolic cages over a period of 2–3 days for quantitative collection of urine and faeces. The activity, measured immediately after administration of ^{51}Cr, was arbitrarily set as the 100% reference value. The ^{51}Cr whole-body retention was measured at given timepoints in the centre of a 200 cm long 4π-geometry whole-body radioactivity detector with liquid organic scintillator in the energy range from 980–3,000 keV (Braunsfurth et al. 1977). The biological half-life of ^{51}Cr was calculated from a triple term exponential fit algorithm to the measured whole-body retention of ^{51}Cr values in a period of 1–100 days after the administration of ^{51}Cr. The ^{51}Cr activity in the excrements and tissues of rats was

measured in the whole-body counter or for longer sensitivity in an 3″ × 3″ NaJ detector (autogamma 5260, Canberra-Packard, Frankfurt, Germany).

The rats were sacrificed by exsanguination from the abdominal aorta while under narcosis with ketamin hydrochloride/xylazin hydrochloride.

Data analysis

The mean ^{51}Cr retention data $R(t)$ from the whole-body counting were fitted by a compartment model with the condition $A_1 + A_2 + A_3 = 100\%$ for the three compartments (Eq. 1).

$$R(t) = A_1 \exp\left(-\ln(2)/T^1_{1/2} t\right) + A_2 \exp\left(-\ln(2)/T^2_{1/2} t\right) + A_3 \exp\left(-\ln(2)/T^3_{1/2} t\right) \quad (1)$$

As starting values for the fit software (Slide Write Plus 6.1, Advanced Graphics Software Inc., Encinitas, USA), the data of Mertz et al. (1965) for the retention of $^{51}CrCl_3$ in rats were used. For the long-term half-life, only a lower and upper threshold could be fitted within the limited observation period. The student t test was used for comparison of whole-body-retention data between different groups of rats. Differences between their mean values were regarded as significant at $P < 0.05$.

Results

After oral administration of ^{51}Cr-picolinate in rats, the apparent intestinal absorption of ^{51}Cr was measured by following the ^{51}Cr whole-body-retention after 7 days (Table 1). $^{51}CrCl_3$ was used as reference compound. This showed that the apparent absorption of ^{51}Cr was significantly lower for $CrPic_3$ as compared to $CrCl_3$ ($P < 0.05$). However, as most of the absorbed Cr from $CrPic_3$ was excreted into the urine within the first 2 days after administration, the real absorption of $CrPic_3$ was substantially higher (Table 1).

It should be noted that the specific activity of synthesized ^{51}Cr-picolinate was limited, and the used chromium dose could only be higher than the assumed physiological dose of chromium in rats. However, so far no dose effect has been found in any of the previous studies with Cr application in rats. This phenomenon was demonstrated here again by the use of $CrCl_3$ as test compound. In fact, in the dose range of 0.01–20 µg Cr a very low and constant intestinal absorption was found (Fig. 1).

Following i.p. and i.v.-injection of $CrPic_3$, almost identical ^{51}Cr-whole-body-retention curves were obtained. The lower threshold for the long half-life was found from a 2-compartment fit, while the upper threshold of $T_{1/2}{}^3$ results from a 3-term fit with fixed parameters $T^1_{1/2}$ and $T^2_{1/2}$ from the 2-term fit and 5.9 days, respectively. With this upper threshold for $T^3_{1/2}$, the final 3-compartment fit resulted in the three pool sizes and their respective half-lifes of ^{51}Cr-retention (see Table 2). A striking feature for $CrPic_3$ is the fast excretion of ^{51}Cr by the kidney. The fast urine excretion may document a significant difference in the metabolism of $CrPic_3$ compared to more ionic chromium compounds such as $CrCl_3$. A small

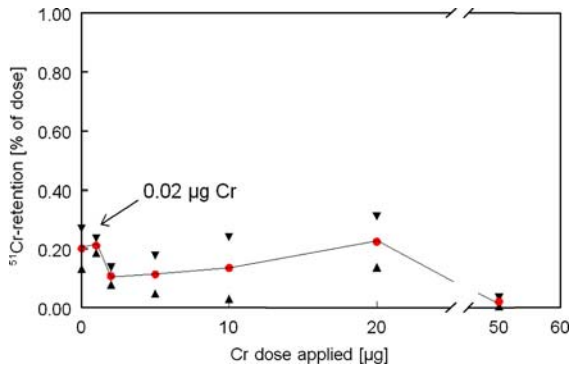

Fig. 1 Intestinal absorption of ^{51}Cr from oral $CrCl_3$ is independent from the dosage (0.01–20 µg Cr)

Table 1 Whole-body-retention, WBR urine or faecal excretion of ^{51}Cr in rats after oral or parenteral application of ^{51}Cr-labelled compounds (8 µg Cr)

	n	7 days-WBR (% of dose)	48 h-urine (% of dose)	Absorption (% of dose)
$CrPic_3$	5	0.079 ± 0.016	1.08 ± 0.075	1.16 ± 0.32
$CrCl_3$	9	0.203 ± 0.116	0.36 ± 0.28	0.55 ± 0.28

Table 2 Whole-body retention parameters after administration of $CrPic_3$ or $CrCl_3$

Compound	Transport-pool		Transit-pool		Storage pool	
	A_1 (%)	$T_{1/2}{}^1$ (days)	A_2 (%)	$T_{1/2}{}^2$ (days)	A_3 (%)	$T_{1/2}{}^3$ (days)
$CrPic_3$ i.p.	96	0.17 ± 0.04	2.5 ± 1.2	5.1 ± 2.7	1.58 ± 0.09	$47 < T_{1/2} \leq 100$
$CrPic_3$ i.v.	88	0.01 ± 0.01	10.5 ± 1.6	1.3 ± 0.2	1.66 ± 0.06	$10 < T_{1/2} \leq 100$
$CrCl_3$ i.p.	22	0.28 ± 0.07	13.0 ± 1.7	4.2 ± 1.2	64.6 ± 0.5	$104 < T_{1/2} \leq 150$

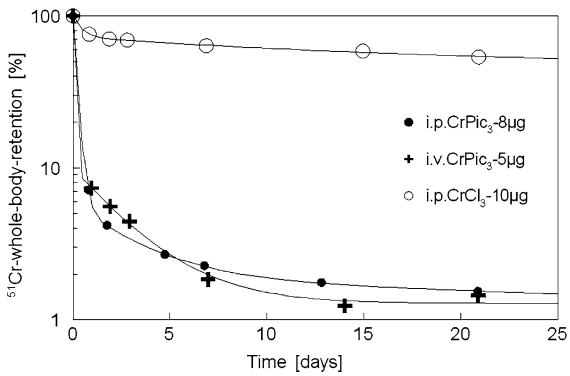

Fig. 2 ^{51}Cr-whole-body retention from $CrPic_3$ i.p. or i.v. and $CrCl_3$ i.p. in groups of rats ($n = 4$–5).The respective half-lives were calculated from a 3-compartment model

fraction of ^{51}Cr was also found in faeces, indicating the biliary excretion of chromium from $CrPic_3$.

After i.p. injection of $CrCl_3$, a different whole-body-retention curve became obvious. The short half-lives were much longer for chromium chloride as for $CrPic_3$ (Fig. 2), documenting the less pronounced urine excretion of Cr from $CrCl_3$. In the dose range from 0.01 to 5 µg Cr/rat, no dose effect was found on the whole-body-retention after i.p. administration (data not shown).

Following the i.p. administration of $CrPic_3$ rats were sacrificed in time intervals ranging from 2 h upto 7 days. Moreover, a reference group of rats received 50 µl of rat serum i.p. which was in vitro labelled with a tracer dose of $^{51}CrCl_3$ (Fig. 3). Although the distribution of ^{51}Cr from these two test compounds

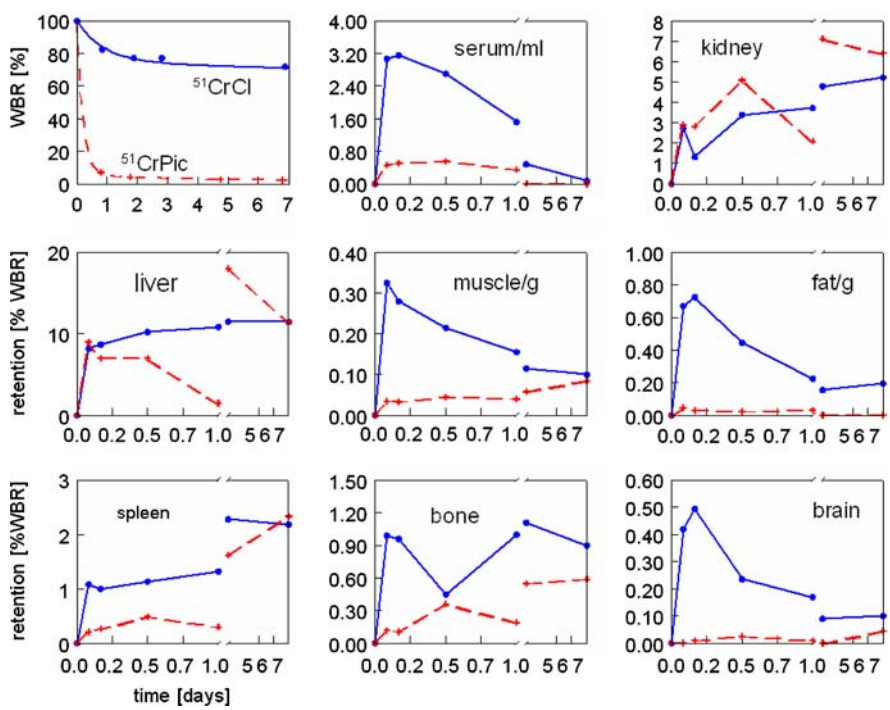

Fig. 3 ^{51}Cr-retention (% of the whole-body-retention at that time) in organs and tissue of rats after $CrPic_3$ i.p. (16 µg Cr/rat) or $CrCl_3$ (tracer dose, preincubated with rat serum). Each time point represents the mean value of two rats

was different in the initial 24 h, these differences seemed to equalize after 3–7 days. Obviously, Cr was stored preferentially in the liver, kidney, spleen and bones, and less in fat, brain and muscle.

Discussion

$CrPic_3$ is widely used in animal and human studies. However, the improved bioavailability of $CrPic_3$ has never been demonstrated directly. We therefore investigated in the present study the absorption, retention, tissue distribution and excretion of Cr from $CrPic_3$ in rats by applying direct and quantitative methods. By using the same whole-body counting technique we found pharmacokinetic data for the reference compound $CrCl_3$ that are in close agreement with earlier studies (Mertz et al. 1965; Onkelinx 1977).

The real intestinal absorption (whole-body retention and urine excretion) of Cr from $CrPic_3$ was found twice as high compared to $CrCl_3$, however, a large fraction of absorbed $CrPic_3$ is located in a transport-pool directed to the kidney excretion. Therefore, in the initial 24 h after oral dosage, most tissues (muscle, fat, bone and brain) display higher ^{51}Cr tissue concentration from $CrCl_3$ than from $CrPic_3$.

Upto now, $CrPic_3$ has been regarded as a relatively well absorbed form of chromium with a bioavailability of 2–5% (Vincent 2001; Hummel et al. 2007) based on rat studies (Anderson et al. 1996) and studies in human volunteers. Particularly in the latter a relative high excretion of Cr in urine was noted after supplementation with $CrPic_3$, as compared to $CrCl_3$ and nutritional Cr (Clancy et al. 1994; Gargas et al. 1994). This high urine excretion has recently been confirmed in a study in volunteers comparing four different commercial chromium supplements (DiSilvestro and Dy 2007). From a single oral dose of 200 μg Cr, $CrPic_3$ produced the highest urinary Cr excretion at the 24 h time point. In this and in other studies the urinary excretion of Cr is uncritically used as a reliable measure of Cr absorption and bioavailability. In the present work we found evidence that the metabolism of $CrPic_3$ in rats may be different to the more ionic chromium chloride. Following this view, high urinary Cr from oral $CrPic_3$ would reflect not only a higher absorption but also a poor tissue uptake.

The mechanisms involved in the intestinal chromium absorption are not well understood (Ducros 1992). Some authors found that the absorption of Cr^{3+} in rats is not saturable (Donaldson and Barreras 1966; Dowling et al. 1989). In agreement with this we have also not found any saturation effect after dosing 0.02–20 μg/rat in the form of $CrCl_3$ by gastric-gavage, which probably indicates that a passive diffusion process may be involved in intestinal absorption. Clearly, this may be different in humans where an inverse relationship between dietary chromium intake and the degree of Cr absorption was reported (Anderson and Kozlovsky 1985).

The stable chromium complex $CrPic_3$ may even have a different absorption mechanism than more ionic chromium compounds. It has already been discussed earlier that $CrPic_3$ may be absorbed as intact molecule by a completely different absorption process (Gammelgaard et al. 1999; Hepburn and Vincent 2002). After uptake, the interaction with cells and plasma proteins may be slower than with absorbed ionic Cr^{3+} and therefore is the majority of $CrPic_3$ excreted directly into the urine. Only after hepatocellular uptake, Cr may be released from the $CrPic_3$ complex. The efficient degradation of $CrPic_3$ by hepatocytes has been demonstrated previously (Kareus et al. 2001). The fast elimination of $CrPic_3$ by the kidney may be responsible for the very short half-life after i.v. injection. Only a minor fraction of absorbed $CrPic_3$ may then be metabolized in the liver, resulting in a physiological form of Cr, which enters the cellular Cr pool and is finally stored in the body with a half-life of >100 days. The term "bioavailability" should therefore be discussed very carefully regarding the low retention of Cr from $CrPic_3$ in the body. "Bioavailability", in its pharmacological meaning, denotes the extent to which a substance is reaching its site of action in the body by way and rate of systemic circulation. For chromium, the believed site of action is the insulin receptor on the surface of insulin-dependent cells (e.g. in fat and muscle tissue). If most of the absorbed $CrPic_3$ does not enter the physiological chromium pool in vivo, the higher intestinal absorption from $CrPic_3$ is mostly irrelevant as far as the medical benefit in chromium supplementation is concerned. The results of the present study could also indicate that the bioavailability of Cr compounds could generally differ because of different distribution pathways in vivo rather than because of varying intestinal absorption rates.

As documented by the time-dependent storage of chromium in tissues from 1 h to 7 days, the distribution of Cr from $CrCl_3$ and $CrPic_3$ resulted in similar tissue concentrations. This could indicate the existence of regulated transport pathways, an argument which would support the role of chromium as an essential trace element. The discussion on the benefit of chromium supplementation, and particularly of $CrPic_3$, is so far hampered by a high degree of polarization between "believers" and "non-believers". In the US, the dietary guidelines for Cr intake were recently lowered to 35 μg for an adult male, and 25 μg for an adult female, because chromium deficiency seems rare in the normal population (Trumbo et al. 2001). It seems clear that supplementing Cr-sufficient subjects will have no positive effects on glucose or lipid metabolism. However, the situation in patients with diabetes mellitus may be different. Hyperglycaemia could stimulate the urinary loss of Cr, which could lead over time to the occurrence of severe Cr deficiency, which then can diminish insulin receptor function ending up in insulin resistance, diabetes type 2. For many years, the discussion on the benefit of chromium supplementation was dominated by skepticisms. The FDA has reviewed 29 relevant human studies published through the year 2000 on $CrPic_3$ as Cr supplement in subjects with risk of type 2 diabetes and found only one small study suggesting that $CrPic_3$ may reduce the risk of type 2 diabetes (Trumbo and Ellwood 2006; Cefalu et al. 1999). However, newer publications seem to favour a positive effect of chromium supplementation in diabetes. A meta-analysis of the literature published upto 2006 concluded that Cr supplementation significantly improved glycosylated haemoglobin and fasting glucose in type 2 diabetes (Balk et al. 2007). Also actual publications provided evidence of positive effects in diabetic patients due to $CrPic_3$ supplementation (Martin et al. 2006; Albarracin et al. 2008). Moreover, the streptozotoxin model to introduce diabetes mellitus in rats seems to offer a valuable system to study the effects of chromium supplements in more detail (Sahina et al. 2007; Jain et al. 2007). Both these studies showed clearly positive effects of Cr supplements on various parameters in diabetes. Interestingly, $CrNic_2$ appeared to be more effective than $CrPic_3$ in lowering blood levels of proinflammatory cytokines, oxidative stress and lipids in diabetic rats (Jain et al. 2007). Although the reason for the difference between the two Cr compounds is unclear at the moment it may be connected to different intestinal absorption. Alternatively it may be a specific in vivo effect as discussed before. Based on urine excretion $CrNic_2$ was less well absorbed than $CrPic_3$ in humans (Disilvestro and Dy 2007). In rats, the ^{51}Cr concentration in tissue and urine measured 1–12 h after oral application was higher when $^{51}CrNic_2$ was applied (Olin et al. 1994). However, these short-time experiments can not provide a definite picture on the bioavailability of chromium compounds in comparison, and the low urine excretion from $CrPic_3$ compared to $CrCl_3$ in the Olin study is in direct conflict to our results.

In the present study we have found a very low retention of Cr form oral $CrPic_3$ in rats (<0.1%). The real absorption of this compound was much higher (1%) but most of the absorbed ^{51}Cr from $CrPic_3$ was excreted into the urine within 2 days after administration. Nevertheless, $CrPic_3$ provides bioavailable Cr to all tissues (Lindemann et al. 2004). More studies on the transport, the biochemical function and storage of chromium from different Cr compounds are emphasized to provide the basis for a more rational decision of whether chromium supplementation is a useful strategy in patients at risk for diabetes mellitus.

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