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Recent advances in the nutritional biochemistry of trivalent chromium

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The nutritional biochemistry of trivalent Cr has been a poorly understood field of study; investigations of the biochemistry of the other essential transition metals have not proven as problematic. Despite over four decades of endeavour, only recently has a picture of the role of Cr potentially started to be defined. The biologically-relevant form is the trivalent ion. Cr^{3+} appears to be required for proper carbohydrate and lipid metabolism in mammals, although fortunately Cr deficiency is difficult to achieve. Conditions that increase circulating glucose and insulin concentrations increase urinary Cr output. Cr is probably excreted in the form of the oligopeptide chromodulin. Chromodulin may be the key to understanding the role of Cr at a molecular level, as the molecule has been found to bind to activated insulin receptor, stimulating its kinase activity. A mechanism for the action of chromodulin has recently been proposed; this mechanism can serve as a potential framework for further studies to test the role of Cr in metabolism. An examination of the nutritional supplement chromium picolinate illustrates some of the difficulties associated with these biochemical studies.

Chromium: Chromodulin: Chromium picolinate

In the last decade Cr has become amazingly popular as a nutritional supplement, weight-loss agent and muscle-development agent. Among mineral supplements products containing Cr are second in sales only to Ca-containing products (Nielsen, 1996). However, this popularity is not reflected in the level of understanding of how Cr functions in the body or even of whether the element is essential. With one exception, the first-row transition elements from V to Zn (and additionally the heavier transition elements Mo and W) have been shown to be essential for at least one form of life. Additionally, a biomolecule containing each of these metals, except one, has been crystallized and its three-dimensional structure determined. The exception is Cr.

While it is generally accepted that Cr is an essential element, the evidence is strongly supportive, but not definitive (Vincent, 2001). Four types of evidence have been presented to support the role for Cr as a trace nutrient for mammals: (1) five patients on total parenteral nutrition (before supplemental Cr was added to total parenteral nutrition solutions) developed symptoms of adult-onset diabetes that were reversed by the addition of Cr to the total parenteral nutrition solution (Jeejeebhoy, 1999); (2) rats fed a low-Cr sucrose-based diet have increased areas under the curve for insulin in glucose tolerance tests, suggesting the development of insulin resistance (Striffler *et al*. 1995, 1999); (3) Cr absorption is inversely proportional to dietary intake in human subjects (Anderson & Kozlovsky, 1985); (4) increases in serum glucose are accompanied by increases in urinary Cr excretion, while conditions that alter glucose metabolism (including pregnancy, type 2 diabetes and other metabolic stresses) are associated with alterations in urinary Cr output (Kozlovsky *et al*. 1986; Anderson *et al*. 1990; Morris *et al*. 1993). These associations suggest a relationship between normal glucose metabolism and Cr, probably associated with insulin action.

However, each of these sets of evidence is problematic. For example, Cr absorption in rats (Anderson & Polansky, 1995), in contrast to human subjects, is not inversely proportional to intake. Increased urinary excretion of Cr may only reflect the effects of changes in the levels of Fe mobilization in response to insulin. Incidences of diagnosed potential Cr deficiency in human subjects are limited to five cases that lack consistent relationships between the Cr in the total parenteral nutrition, time on total parenteral nutrition before symptoms, serum Cr levels and symptoms

Abbreviation: $Cr(pic)_3$, chromium picolinate.

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(Stearns, 2000). For these reasons the reversal of symptoms associated with Cr supplementation is the only generally accepted indicator of Cr deficiency. A biomarker of Cr status is urgently needed. Studies undertaken before 1990 that examined the effects of Cr-deficient diets are flawed by methodological concerns (Vincent, 2001).

Fortunately, the data suggest that generating Cr deficiency in human subjects is extremely difficult. The dietary guidelines for Cr intake recommended by the Food and Nutrition Board of the US National Academy of Sciences have been lowered from 50–200 μg/d for an adult to 35 μg/d for an adult male and 25 μg/d for an adult female (Trumbo *et al*. 2001). The new guideline values for Cr are adequate intakes, a recommended intake based on the intakes of groups of healthy individuals that are assumed to be adequate when there is sufficient data to establish a recommended daily allowance. Thus, these limits are set at the average intake for Americans (for data on average intake and Cr balance, see Bunker *et al*. 1984; Gibson & Scythes, 1984; Anderson & Kozlovsky, 1985; Offenbacher *et al*. 1986; Anderson *et al*. 1993), indicating that few Americans should be Cr deficient.

Chromium picolinate

Although the first studies that suggested that chromium picolinate ($Cr(pic)_3$) could have beneficial effects on body mass and composition were only published in 1989 (Evans, 1989), the nutritional supplement has become amazingly popular. For example, products containing the supplement generated approximately US $\$0{\cdot}5 \times 10^9$ in sales in 1999 (Mirasol, 2000). However, studies of $Cr(pic)_3$ in healthy individuals conducted since the initial reports have failed to support the early findings (Hellerstein, 1998). A recent review has examined human studies investigating the effects of $Cr(pic)_3$ on body composition and concluded that 'the supplement has no demonstrated effects on healthy individuals, even when taken in combination with an exercise program' (Vincent, 2003). Other researchers have come to similar conclusions (Clarkson, 1997; Kreider, 1999; Lukaski, 1999), as have recent meta-analyses (Nissen & Sharp, 2003; Pittler *et al*. 2003). There have also been claims that suggest that $Cr(pic)_3$ has beneficial effects on plasma glucose and insulin concentrations and other blood variables in healthy subjects. These claims have not been substantiated, as shown by another recent review (Vincent, 2001) and meta-analysis (Althuis *et al*. 2002).

Only 6 years after the initial report of potentially beneficial effects from $Cr(pic)_3$ supplementation, Wetterhahn and coworkers (Stearns *et al*. 1995) reported the first chemical evidence for concerns over the use of $Cr(pic)_3$. The complex generated chromosome damage in a Chinese hamster ovary cell model. Subsequently, damage was demonstrated in murine macrophages (Bagchi *et al*. 1997), and another study using the same cell line observed oxidative damage associated with $Cr(pic)_3$ (Bagchi *et al*. 2002). Stearns and colleagues (Stearns *et al*. 1995; Manygoats *et al*. 2002) in continuing work with the Chinese hamster ovary model have observed mitochondrial damage and apoptosis generated by the supplement (Manygoats *et al*. 2002) and have found that the supplement is mutagenic (Stearns *et al*. 2002). The effects have been postulated to arise from the released picolinate ligand (Stearns *et al*. 1995; Manygoats *et al*. 2002) or from reactive oxygen species catalytically generated by the intact complex (Speetjens *et al*. 1999*a*; Sun *et al*. 2000). Physiologically-relevant concentrations of Cr as $Cr(pic)_3$ (e.g. 120 nM) and of biological reducing agents such as ascorbic acid and thiols have been shown by the author's group to result in catalytic production of reactive oxygen species, which cleaved DNA (Speetjens *et al*. 1999*a*; Sun *et al*. 2000). Most forms of Cr do not generate such species in the absence of a strong oxidant such as peroxide. Hence, these studies are consistent with investigations that demonstrated that mutagenic forms of trivalent Cr possessed chelating ligands containing pyridine-type N or other imine-N (e.g. 2,2′-bipyridine, phenanthroline and Schiff bases) coordinated to the metal and that they generated reactive oxygen species (Sugden *et al*. 1992). Cr compounds that do not have imine ligands lack the DNA cleaving activity in the presence of biological reducing agents (Speetjens *et al*. 1999*b*). Alternatively, neutral $Cr(pic)_3$ could serve as a vehicle for the transport of picolinate to cells. Consequently, for these mechanisms to lead to marked cell damage $Cr(pic)_3$ needs to enter cells intact and remain intact long enough to produce a substantial quantity of reactive oxygen species or then degrade releasing picolinate. Recently, Vincent and coworkers (Hepburn & Vincent, 2002, 2003) have shown that $Cr(pic)_3$ is able to pass rapidly from the bloodstream and enter cells intact, although the lifetime of the complex in cells is short. In these studies the appearance and distribution of Cr in tissues after intravenous injections of $Cr(pic)_3$ are very similar to those found when $Cr(pic)_3$ is administered orally (Olin *et al*. 1994). In hepatocytes Cr from $Cr(pic)_3$ first appears in the nucleus and mitochondria, then the cytosol, and finally the lysosomes and microsomes; however, the complex has no propensity to bind to DNA. Kelley and coworkers (Kareus *et al*. 2001) have found that hepatocyte microsomes can catalytically modify the picolinate ligands, which would result in Cr release. While Cr from administration of the supplement can accumulate in the kidneys and liver (Anderson *et al*. 1997*a*), it does not accumulate as $Cr(pic)_3$ (Hepburn & Vincent, 2002, 2003).

Isolated incidents of deleterious effects of $Cr(pic)_3$ supplementation have been reported (Huszonek, 1993; Wasser & D'Agati, 1997; Cerulli *et al*. 1998; Martin & Fuller, 1998; Fowler, 2000). The nature of these incidents makes their importance difficult to ascertain. In contrast, no acute toxic effects were observed in rats fed diets containing ≤100 mg Cr as $Cr(pic)_3$/kg diet for 24 weeks (Anderson *et al*. 1997*a*). However, the potential effects of oxidative damage were not investigated. No toxic effects of $Cr(pic)_3$ supplementation were noted in any of the studies covered by the review articles mentioned previously, which in total monitored hundreds of subjects (Vincent, 2001, 2003). There have not yet been any studies that have examined the effects, positive or negative, of long-term (>1 year) use of $Cr(pic)_3$.

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However, human and animal studies that have looked for DNA damage and oxidative damage have started to be published. The level of 5-hydromethyluracil in the blood serum is a marker of the extent of oxidation of the DNA base thymine; after oxidation, the modified base is enzymically removed and subsequently appears in the serum. The repair of this damage has a considerable error rate, giving rise to mutations. There was no observed effect on 5-hydroxymethyluracil levels in ten obese women given 400 μg Cr as $Cr(pic)_3$/d for 8 weeks (Kato *et al*. 1998). In contrast, Vincent and coworkers (Hepburn *et al*. 2003*a*) found that rats given an intravenous injection of $Cr(pic)_3$ daily for 60 d had elevated levels of urinary 8-hydroxydeoxyguanosine and elevated levels of peroxidized lipids. Both direct DNA oxidation and indirect DNA damage via lipid peroxidation resulting from $Cr(pic)_3$ administration provide potential pathways for the chromosome damage (Stearns *et al*. 1995) and, more recently, the mutations (Stearns *et al*. 2002) seen in cell culture studies. The quantities of Cr used in this study were high, but establish that such damage is possible *in vivo*. Also, a recent preliminary report (Mahboob *et al*. 2002) has indicated that $Cr(pic)_3$ causes oxidative damage when given orally to rats in quantities equivalent to the intakes of human subjects taking commercial supplements. Potentially-deleterious *in vivo* effects of $Cr(pic)_3$ have been examined recently by O'Donnell and Vincent and coworkers using *Drosophila melanogaster* (Hepburn *et al*. 2003*b*). $Cr(pic)_3$, but not $CrCl_3$, at ≤260 μg Cr/kg food (approximately equivalent to that received by a human subject taking daily $Cr(pic)_3$ supplement containing 200 μg Cr) was found to lower the success rate of pupation and eclosion and to arrest development of pupae in a concentration-dependent manner. X-linked lethal analysis has indicated that the supplement greatly enhances the rate of appearance of lethal mutations and dominant female sterility. Subsequently, Vincent and coworkers (DDD Hepburn and JB Vincent, unpublished results) examined polytene chromosome arms of nuclei from cells of salivary glands from third instar larval *Drosophila*; these larvae were the progeny of male and female *Drosophila* maintained on $Cr(pic)_3$-containing food (260 μg Cr/kg food). Although the progeny were never exposed to the supplement, >50% of the chromosome arms had chromosomal aberrations and rearrangements. In contrast, no aberrations or rearrangements were observed in chromosome arms of progeny from adults on food without the supplement.

In March 2003 the Expert Group on Vitamins and Minerals of the UK Joint Food Standards and Safety Group requested that the health supplement industry should voluntarily withdraw $Cr(pic)_3$-containing products, while also consulting on a ban on the use and sale of $Cr(pic)_3$ in the UK. Currently, the US Food and Drug Administration, working with the US National Academy of Sciences, is studying the potential regulation of $Cr(pic)_3$.

Chromium and type 2 diabetes

While Cr supplementation of the diet of healthy individuals appears to have no statistically significant effects, the situation with supplementation of subjects with type 2 diabetes may be very different. As Cr is probably an essential trace element, supplementary levels of Cr would be expected to have little if any effect on variables such as body mass or body composition if subjects consume Cr-sufficient diets. However, the administration of pharmacological amounts of Cr could result in effects that potentially could lead to altered Cr status, especially for subjects with altered metabolisms. Type 2 diabetes (Morris *et al*. 1999) and pregnancy (Morris *et al*. 1995) are examples of conditions that lead to increased urinary Cr loss, which with time could result in a decrease in Cr status, although this outcome has not been proven. Thus, individuals with these conditions could potentially benefit from Cr supplementation. Additionally, because these individuals have lowered insulin sensitivity and could potentially benefit from increased Cr loading of chromodulin (thought to be the naturally-occurring biologically-active form of Cr; see p. 44), resulting in increased insulin signalling, administration of pharmacological amounts of Cr could be beneficial. Similarly, a therapeutic agent (such as the trinuclear biomimetic complex; see p. 45) that mimics chromodulin's action could be particularly useful in treating their insulin insensitivity.

The effects of Cr in subjects with type 2 diabetes are less certain than those in healthy subjects (in whom no significant effects are observed). A meta-analysis of studies involving diabetic subjects revealed that 'A study of 155 diabetic subjects ... showed that chromium reduced glucose and insulin concentrations; the combined data from ... the other studies did not' (Althuis *et al*. 2002). The placebo-controlled study of Anderson *et al*. (1997*b*), which involved 155 subjects in China, is the largest reported study of diabetic subjects. The subjects received 0, 200 or 1000 μg Cr daily for 4 months. At the higher levels of Cr subjects had reduced fasting serum glucose, insulin and total cholesterol, and lower 2 h insulin and glucose concentrations after a glucose challenge. Subjects also possessed lower glycated Hb A_1 levels. Follow-up studies in China (Cheng *et al*. 1999) yielded results in accord with the initial study. The original study has been analysed in detail by Hellerstein (1998). Before 2002 the consensus from double-blind placebo-controlled studies of the effects of Cr supplementation for 6–16 weeks in subjects with type 2 diabetes was that supplementation had no effect (Vincent, 2001). In all these studies ≤200 μg Cr was administered daily. However, a recent double-blind crossover study in India of subjects with type 2 diabetes indicated that Cr supplementation (400 μg Cr/d) for 12 weeks lowered serum insulin and glucose levels (Ghosh *et al*. 2002). Anderson (1998, 2000) has reviewed studies of the effects of Cr supplementation in subjects with type 2 diabetes; generally, only studies using <200 μg Cr daily reported no effects from supplementation, leading the reviewer to postulate that larger quantities of Cr can have beneficial effects in subjects with type 2 diabetes. Thus, positive effects from Cr supplementation of subjects with type 2 diabetes potentially have only been seen in very recent studies (after 1996) that utilized large pharmacologically-relevant quantities of Cr.

Importantly, the findings of the studies using >200 μg Cr/d are supported by the findings of studies that used

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model rats. A trinuclear biomimetic complex (see p. 45) was found to have beneficial effects on Zucker obese rats, models for the early stages of type 2 diabetes (Sun *et al*. 1999, 2002), while smaller, but significant ($P \leq 0{\cdot}05$), effects were also noted in healthy rats. Cefalu *et al*. (2002) observed beneficial effects of $Cr(pic)_3$ administration (18 μg Cr/kg body mass daily, equivalent to 540 μg for a 60 kg subject) on insulin sensitivity in a rat model for type 2 diabetes and CVD. Thus, the continuation of rat and human studies is required in order to further elucidate the potential use of Cr administration as an adjuvant therapy for type 2 diabetes.

Additionally, one study of the effects of Cr on gestational diabetes has been reported (Jovanovic *et al*. 1999). In women (average body mass 82–84 kg) who received 0, 4 or 8 μg Cr/kg body mass daily it was found that both Cr-supplemented groups had significantly ($P \leq 0{\cdot}05$) lower plasma insulin and glucose levels. If the findings of this single study are confirmed by additional studies, this result would have important implications for the treatment of this condition. Recently, studies of the effects of Cr supplements on steroid-induced diabetes have generated interesting results (Ravina *et al*. 1999*a*,*b*), including improvements in plasma glucose levels. Although these studies still need to be followed up by larger investigations, the findings are supported by those of a recent study of rats treated with dexamethasone (Kim *et al*. 2002). The dexamethasone-treated rats receiving approximately 4 mg Cr daily had lower fasting serum insulin levels and lower insulin, triacylglycerol and glucose areas under the curve in glucose or insulin challenges.

A mechanism for the action of chromium and an active chromium-containing biomolecule

Investigations over the last two decades have suggested that there is a naturally-occurring biomolecule that binds trivalent Cr that can explain how Cr is involved in carbohydrate and lipid metabolism. This molecule, chromodulin (originally termed low-molecular-weight Cr-binding substance), is a naturally-occurring oligopeptide composed of glycine, cysteine, aspartate and glutamate with the carboxylates comprising more than half the total amino acid residues (Yamamoto *et al*. 1987; Davis & Vincent, 1997*b*). Despite its small size (molecular weight approximately 1438 for the bovine liver material), the molecule tightly binds four equivalents of Cr^{3+}. The binding is quite tight (association constant approximately 10^{21} M^4) and highly cooperative (Hill coefficient, n 3·47; Sun *et al*. 2000). Spectroscopic studies suggest that the Cr^{3+} comprise an anion-bridged multinuclear assembly supported by carboxylates from the oligopeptide (Davis & Vincent, 1997*b*; Jacquamet *et al*. 2003). Chromodulin has been isolated from the liver or kidney of several mammals and purified. A related Cr-containing oligopeptide (M-low-molecular-weight Cr-binding substance) has been isolated from bovine colostrum, which comprises the same amino acids, but in distinctly different ratios, and also stimulates insulin-dependent glucose metabolism in rat adipocytes (Yamamoto *et al*. 1988). The relationship between the milk and liver oligopeptides is deserving of additional study and suggests the possibility that other carboxylate-rich oligopeptides might exist and play a role in Cr transport or function.

The oligopeptide is maintained *in vivo* in the apo form (Yamamoto *et al*. 1987; Davis & Vincent, 1997*b*). This observation has resulted in the suggestion that chromodulin may play a role in Cr detoxification. However, injection of Cr^{3+} or chromate into mice does not stimulate the production of apochromodulin (Yamamoto *et al*. 1984). Chromodulin does carry Cr into the urine after the intake of large dosages of trivalent and hexavalent Cr (Wada *et al*. 1983; Clodfelder *et al*. 2001) and can, therefore, assist in Cr detoxification.

Another potential function for chromodulin has been identified by the author's laboratory. Chromodulin has been shown to activate the tyrosine kinase activity of insulin-activated insulin receptor (Davis *et al*. 1997; Davis & Vincent, 1997*a*) and to activate a membrane phosphotyrosine phosphatase in adipocyte membranes (Davis *et al*. 1996). For example, the addition of bovine liver chromodulin to rat adipocytic membranes in the presence of 100 nM-insulin results in an up to eight-fold stimulation of insulin-dependent protein tyrosine kinase activity that is concentration dependent, while no activation of kinase activity is observed in the absence of insulin (Davis & Vincent, 1997*a*). The dependence of the kinase activation on the concentration of chromodulin can be fitted to a hyperbolic curve to give dissociation constants of approximately 875 pM. Cr plays a crucial role in the activation of insulin receptor kinase activity by chromodulin (Davis & Vincent, 1997*a*). Apochromodulin does not activate insulin-dependent tyrosine kinase activity in rat adipocyte membranes. Titration of apochromodulin with Cr^{3+} results in the total restoration of the ability to activate kinase activity; approximately four Cr^{3+} per oligopeptide are required for maximal activity. This reconstitution of chromodulin's activation potential is specific to Cr; addition of other biologically-relevant metals does not restore activity to the apo-oligopeptide.

Based on these results, it has been proposed by the author's laboratory that chromodulin functions as part of a unique autoamplification system for insulin signalling (Vincent, 2000*b*,*c*). In this mechanism apochromodulin is stored in insulin-sensitive cells. In response to increases in blood insulin concentrations insulin binds to its receptor, bringing about a conformation change that results in the autophosphorylation of tyrosine residues on the internal side of the receptor. This process transforms the receptor into an active tyrosine kinase and transmits the signal from insulin into the cell. In response to insulin Cr is moved from the blood to insulin-sensitive cells. Here, the Cr flux results in the loading of apochromodulin with Cr. The holochromodulin then binds to the receptor, presumably assisting in the maintenance of the receptor in its active conformation, amplifying the receptor's kinase activity. When the signalling is to be turned off, a drop in blood insulin levels facilitates relaxation of the conformation of the receptor, and the holochromodulin is excreted from the cell into the blood. Ultimately, chromodulin is efficiently excreted in the urine. The Fe-transport protein transferrin has recently been shown to be responsible for maintaining

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Cr^{3+} levels in the blood plasma and for transporting Cr to tissues in an insulin-responsive manner (Vincent, 2000*a*; Clodfelder *et al*. 2001). The basis of the name chromodulin is the similarity of this proposed mechanism of action to that of the Ca-binding protein calmodulin (Vincent, 2000*b*). Both molecules bind four equivalents of metal ions in response to a metal ion flux; however, the four Ca^{2+} that bind to the larger protein calmodulin lie in mononuclear sites. Both holoproteins selectively bind to kinases and phosphatases, thus stimulating their activity.

A potential chromium therapeutic

The existence of a multinuclear trivalent Cr–carboxylate assembly in an active biomolecule has spurred an interest in the synthesis and characterization of multinuclear oxo(hydroxo)-bridged trivalent Cr–carboxylate assemblies (Vincent, 2000*b*). Well-characterized water-soluble assemblies have been tested by the author's laboratory for the ability to stimulate insulin receptor's tyrosine kinase ability in a manner similar to chromodulin. The trinuclear cation $[Cr_3O(O_2CCH_2CH_3)_6(H_2O)_3]^+$ was found *in vitro* to mimic the ability of chromodulin to stimulate this activity (Davis *et al*. 1997); thus, the cation is a functional biomimetic of chromodulin. Consequently, the trinuclear cation has been proposed as a potential therapeutic agent to increase insulin sensitivity. The synthetic complex has other several potential benefits over the natural material. For example, it is inexpensive to synthesize and can be readily prepared in bulk. Also, while chromodulin is susceptible to hydrolysis, especially in the presence of acid, the synthetic material can be recrystallized from dilute mineral acid (Johnson *et al*. 1981) and should consequently survive oral ingestion. The biomimetic cation remains intact after injection into the bloodstream and is subsequently taken up intact by cells (Shute & Vincent, 2001, 2002). When given intravenously to healthy rats at a level equivalent to 20 µg Cr/kg per body mass per d for 12 weeks the biomimetic has been shown to lower fasting serum triacylglycerol and total cholesterol levels; administration of similar quantities of propionate by itself had no effect (Sun *et al*. 1999). Subsequently, in healthy rats 24 weeks of intravenous administration of the cation (0–20 µg Cr/kg body mass), resulted in a concentration-dependent lowering of levels of fasting blood plasma LDL-cholesterol, total cholesterol, triacylglycerols and insulin, and of 2 h plasma insulin and glucose levels after a glucose challenge (Sun *et al*. 2002). The cation had little, if any, effect on rats with streptozotocin-induced diabetes (a type 1 diabetes model). However, after 24 weeks of supplementation (20 µg/kg) Zucker obese rats (a model of the early stages of type 2 diabetes) had lower fasting plasma total cholesterol, HDL- and LDL-cholesterol, triacylglycerol and insulin levels and lower 2 h plasma insulin levels (Sun *et al*. 2002). The lowering of plasma insulin concentrations with little effect on glucose concentrations suggests that the cation increases insulin sensitivity. The author's laboratory, as part of an ongoing study, has found that the trinuclear biomimetic complex, when given orally at amounts equivalent to those used in early intravenous studies, has beneficial effects after just 8 weeks of administration (BJ Clodfelder, B Gullick and JB Vincent, unpublished results).

Conclusions

While the evidence is not overwhelming, it suggests that Cr is an essential trace element in mammals, including man, and affects carbohydrate and lipid metabolism through the action of insulin. The daily requirement for human subjects is small, i.e. approximately 30 µg, such that it is difficult for healthy individuals to develop Cr deficiency. Thus, the use of Cr supplements is probably unnecessary for the general public. However, the use of certain Cr supplements, such as $Cr(pic)_3$, is probably harmful. While nutritional supplement levels of Cr do not appear to have beneficial effects, pharmacological quantities of Cr may increase insulin sensitivity in both healthy subjects and subjects with type 2 diabetes. The biomolecule chromodulin may be part of an insulin-potentiating pathway and may explain the requirement for Cr.

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