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Review

Is chromium pharmacologically relevant?

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ABSTRACT

Recent research, combined with reanalysis of previous results, has revealed that chromium can no longer be considered an essential trace element. Clinical studies are ambiguous at best as to whether Cr has a pharmacological effect in humans. Observed effects of Cr on rodent models of insulin resistance and diabetes are best interpreted in terms of a pharmacological role for Cr. Studies on the effects of Cr on rat models of diabetes are reviewed herein and suggest Cr increases insulin sensitivity in peripheral tissues of the rodent models. The lack of effects in human studies may stem from humans receiving a comparably smaller dose than the rodent models. However, given the different responses to Cr in the rodent models, humans could potentially have different responses to Cr.

Contents

Introduction

Over five decades ago, Cr was proposed to be an essential element; however, as a result of recent research and reanalysis of its status, the element currently should only be considered as potentially pharmacologically active [1–3]. In 2002, the National Academies of Sciences (USA) established an adequate intake (AI) value of 30 μg/d for adults, a reduction from a suggested intake of 50–200 μg daily [4]. By definition, the AI indicates that >98% of Americans cannot be considered Cr deficient. Cr has been marketed as a body mass reducing and muscle development agent; however, such marketing claims are no longer allowed in the United States as they are unsupported by experimental data [5]. However, trivalent Cr has also been proposed as a therapeutic agent to increase insulin sensitivity and affect lipid metabolism.

Is chromium pharmacologically active? - Clinical studies

Supplementation with Cr has been proposed to result in beneficial responses in mammals with demonstrated glucose intolerance or insulin insensitivity, including type 2 diabetes, cardiovascular disease, and related conditions. However, studies in humans tend to be negative or at best ambiguous [5]. The clinical studies, while focused primarily on type 2 diabetic subjects, tend to have small subject pools and not be well designed. One study has dominated attention; 185 adult-onset diabetic Chinese patients participated in the study, in which decreases in the concentration of fasting serum glucose, insulin, hemoglobin A1C, and total cholesterol as well as decreased glucose and insulin levels in response to glucose challenges were observed as a result of Cr supplementation in a dose-responsive manner [6]. Unfortunately, attempts to reproduce these results with other populations, including Western populations, have been unsuccessful (for example, refs. [7,8]). Two meta-analyses commissioned by agencies of the United States

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government have generated inconclusive results on whether Cr affects symptoms of type 2 diabetes. Althius et al. [9] in 2002 with funding from the Office of Dietary Supplements of the National Institutes of Health (NIH) identified only four quality studies for analysis and found the results were inconclusive as the combined results except for those of the Chinese study found no effects. Balk et al. [10] in 2007 with funding from the Department of Health and Human Services identified 18 studies. The authors concluded Cr supplementation "may have a modest effect" on glucose metabolism in type 2 diabetics but that "large heterogeneity and the overall poor quality limit the strength of our conclusions". Unfortunately, the positive effects of greatest magnitude used in the analysis came from the 12 studies ranked lowest in quality, including the Chinese study. A trend was observed that commercial industry-sponsored studies were more likely to observe beneficial effects. A recent meta-analysis that benefits from inclusion of reports of clinical studies since 2007 and improved methodology has found no significant effect of Cr supplementation [11]. Consequently, the position of the American Diabetes Association (ADA) is "There is insufficient evidence to support the routine use of micronutrients, such as chromium, . . . to improve glycemic control in people with diabetes" [12].

Is chromium pharmacologically active? – rodent studies

Several rat models of type 2 diabetes have been utilized to examine the effects of Cr(III) administration (Table 1). While the rat studies have been reviewed previously [5], several recently published studies now allow for a more detailed comparison to be made between the effects of Cr on the different models and strains of rats.

Genetic models

Three models have symptoms arising from related mutations; the JCR:LA-cp, Zucker obese, and Zucker diabetic fatty rats all have mutations of the leptin receptor. Leptin is a hormone produced by adipocytes that signals the brain that the appetite should be suppressed. Consequently, as the leptin signaling systems is blocked at the receptor, the JCR:LA-cp and Zucker obese rats become markedly obese and insulin resistant and possess normal or somewhat elevated blood glucose levels and elevated levels of blood insulin, triglycerides, and cholesterols. The Zucker diabetic fatty (ZDF) rats have an additional, uncharacterized mutation that results in male rats developing symptoms very comparable to type 2 diabetes in humans, including elevated blood glucose levels, in addition to the high triglycerides and cholesterol levels. ZDF rats have skeletal muscle insulin resistance that cannot be compensated by increased insulin production by the beta cells of the pancreas. In contrast to the obese models, the ZDF rats have smaller body masses than healthy Zucker rats.

Three studies have appeared using the JCR:LA-cp rats, all by Russell and co-workers utilizing chromium picolinate, [Cr(pic)$_3$] [13–15]. Cr administration (80 μg/kg body mass daily for 8 weeks to 3 months) resulted in no effect on food intake or body mass. Observations on other effects were somewhat inconsistent. Two studies providing Cr for 3 months reported no effect on fasting blood glucose levels but a reduction in fasting insulin levels [14,15]; (JCR:LA-cp rats have normal fasting glucose levels despite their peripheral tissue insulin resistance). Also both studies reported that total cholesterol and total:high-density lipoprotein (HDL) cholesterol ratio were reduced. Triglycerides were examined in one of the studies [14]; levels were reduced, but the reduction was not statistically significant. HDL levels were increased in one study, while areas under the insulin and glucose curves in glucose tolerance tests (GTT) were reduced [14]. In the shortest duration study (8 weeks) [13], [Cr(pic)$_3$] had no effect on fasting glucose or insulin in addition to body mass and food intake. No effect was observed on total cholesterol or triglycerides. Funding, when indicated, was provided by Nutrition21, the major supplier of chromium picolinate.

Four studies have utilized ZDF rats. Jain et al. [16] administered 400 μg Cr/kg body mass daily for 8 weeks as [Cr(pic)$_3$], Cr nicotinate, and Cr dinicocysteinate (CDNC). All the Cr(III) compounds lowered glycated hemoglobin levels, while only CDNC significantly lowered fasting plasma glucose levels. Clodfelder et al. [17] administered Cr3, [Cr_3O(propionate)$_6$(H_2O)$_3$]$^+$, at a daily dose of 1000 μg Cr/kg for 24 weeks. No effects on body mass or food intake were observed. Fasting plasma insulin, but not glucose, was lower. Additionally, total, LDL (low-density lipoprotein), and HDL cholesterol was lower while the total:HDL cholesterol ratio was unaffected. Given the extremely high HDL levels in these rats, the lowering of HDL levels with no increase in total:HDL cholesterol level may actually be beneficial. Glycated hemoglobin levels were also lower at the end of the study. Talpur et al. [18] started with rats 70–75 weeks of age that were administered 40 μg Cr/kg as Cr nicotinate for 3 weeks and then 80 μg/kg for another 3 weeks. Rats on Cr lost less body mass and consumed more food but not water; no effect was observed on fasting blood glucose. Staniek et al. [19] examined the effects of $CrCl_3$, Cr3, and [Cr(pic)$_3$] on metal distribution. $CrCl_3$ and Cr3, but not [Cr(pic)$_3$], at 1000 μg Cr/kg body mass daily for 12 weeks lowered the elevated Cu levels that occur in ZDF rats compared to healthy Zucker rats. Funding for the studies was provided by InterHealth Nutraceuticals [16,18], NIH [17], or the United States Department of Agriculture (USDA) [19].

Four studies have also examined the effects of Cr on Zucker obese rats. While all the studies but one were performed with federal funding, the groups obtained significantly different results. Vincent and co-workers [17,20] provided 20 or 1000 μg Cr/kg daily as Cr3 for 24 weeks, while Mozaffari et al. [21] provided 5000 and 10,000 μg Cr/kg diet as [Cr(pic)$_3$] for 20 weeks. While both groups observed no effects on food intake or body mass, Mozaffari et al. observed no effects on plasma glucose or insulin or glycated hemoglobin. In contrast, Vincent and co-workers [17,20] observed lower fasting insulin but not glucose; lower total, LDL, HDL, and total:HDL cholesterol and triglycerides; and lower glycated hemoglobin. The differences cannot be attributed to the length of the study as Vincent and co-workers examined several of the variables every 4 weeks during the studies. Curiously, the glycated hemoglobion levels in the study by Mozaffari et al. were the same for both the Zucker obese and control Zucker lean rats; thus, they failed to observe the expected (yet small) increase for the Zucker obese rats and consequently might not be expected to observe any effects from Cr administration. Staniek et al. [19] examined the effects of $CrCl_3$, Cr3, and [Cr(pic)$_3$] on metal distribution. Cr3 and [Cr(pic)$_3$], but not $CrCl_3$, at 1000 mg Cr/kg body mass daily for 12 weeks raised Ca levels in the liver; the significance of this observation is unknown. With funding from InterHealth Nutraceuticals, Preuss et al. [22] found no effect on body mass or food intake but lower fasting serum glucose levels and longer life spans from administering a diet containing 2 mg Cr/kg diet as Cr nicotinate for 300 days.

Zucker lean rats notably have also been shown to respond to high doses of Cr. Cr3 at (1000 μg Cr/kg body mass) has been shown to decrease blood insulin levels in GTT tests after 6, 10, 14, and 18 weeks of treatment and to tend to lower fasting blood insulin levels [20]. Similarly, $KCr(SO_4)_2$ in a dose dependent fashion has been shown to reduce fasting insulin concentrations and insulin areas under the curve in glucose tolerance tests [2]. This suggests that Zucker rats, whether healthy, insulin resistant, or diabetic, respond to Cr treatment, although the response apparently is greater in the insulin-resistant and diabetic models.