Biol Trace Elem Res (2012) 150:291–296
DOI 10.1007/s12011-012-9475-9

The Effects of Chromium Picolinate and Chromium Histidinate Administration on NF-κB and Nrf2/HO-1 Pathway in the Brain of Diabetic Rats

Kazim Sahin · Mehmet Tuzcu · Cemal Orhan · Hasan Gencoglu · Mustafa Ulas · Mustafa Atalay · Nurhan Sahin · Armagan Hayirli · James R. Komorowski

Received: 20 April 2012 / Accepted: 28 June 2012 / Published online: 13 July 2012

Abstract The objective of this experiment was to investigate the effects of supplemental chromium picolinate (CrPic) and chromium histidinate (CrHis) on nuclear factor-kappa B (NF-κB p65) and nuclear factor (erythroid-derived 2)-like 2 (Nrf2) signaling pathway in diabetic rat brain. Nondiabetic (n=45) and diabetic (n=45) male Wistar rats were either not supplemented or supplemented with CrPic or CrHis via drinking water to consume 8 μg elemental chromium (Cr) per day for 12 weeks. Diabetes was induced by streptozotocin injection (40 mg/kg i.p., for 2 weeks) and maintained by high-fat feeding (40 %). Diabetes was associated with increases in cerebral NF-κB and 4-hydroxynonenal (4-HNE) protein adducts and decreased in cerebral nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor, alpha (IκBα) and Nrf2 levels. Both Cr chelates were effective to decrease levels of NF-κB and 4-HNE protein adducts and to increase levels of IκBα and Nrf2 in the brain of diabetic rats. However, responses of these increases and decreases were more notable when Cr was supplemented as CrHis than as CrPic. In conclusion, Cr may play a protective role in cerebral antioxidant defense system in diabetic subjects via the Nrf2 pathway by reducing inflammation through NF-κB p65 inhibition. Histidinate form of Cr was superior to picolinate form of Cr in reducing NF-κB expression and increasing Nrf2 expression in the brain of diabetic rats.

Keywords Chromium picolinate/histidinate · NF-κB p65 · IκBα · Nrf2

K. Sahin (✉) · C. Orhan · N. Sahin
Department of Animal Nutrition, Faculty of Veterinary Medicine, Firat University,
23119 Elazig, Turkey
e-mail: nsahinkm@yahoo.com

M. Tuzcu · H. Gencoglu
Department of Biology, Faculty of Science, Firat University, Elazig, Turkey

M. Ulas
Department of Physiology, School of Medicine, Firat University, Elazig, Turkey

M. Atalay
Institute of Biomedicine, Physiology, University of Eastern Finland, Kuopio, Finland

A. Hayirli
Department of Animal Nutrition, Faculty of Veterinary Medicine, Atatürk University, Erzurum, Turkey

J. R. Komorowski
Technical Services and Scientific Affairs, Nutrition 21 Inc., Purchase, NY, USA

Introduction

Neuropathy is one of most commonly occurring diabetic complications with an overall prevalence of 50–60 % in diabetic patients [1]. Some of the functional consequences of diabetic neuropathy could be alleviated by insulin treatment in insulin-dependent diabetes mellitus [2]. Oxidative stress plays an important role in the pathogenesis of diabetes through reactive oxygen species (ROS) that may initiate inflammatory response because they stimulate a number of genes regulating the inflammatory signaling cascades [3]. These genes may be upregulated by ROS-mediated activation of nuclear factor-kappa B (NF-κB), one of the primary transcription factors initiating inflammatory response and contributing to inflammatory damage in chronic diseases including diabetes [4]. It mediates numerous inflammatory

pathways in multiple cells and organ systems. Inflammation is now recognized to exacerbate many neurodegenerative conditions including diabetic neuropathy [5]. Inhibition of NF-κB activity in spinal glia alleviates pain behaviors in rats with chronic nerve constriction injuries [6]. Nuclear factor erythroid 2-related factor 2 (Nrf2), involved in combating against oxidative stress and neuroinflammation, is a basic leucine zipper transcription factor known to regulate the expression of a number of detoxifying and antioxidant genes. This has also been claimed to regulate various inflammatory processes [7, 8]. Several studies ascertained pivotal role of Nrf2 in modulation of inflammation in insulin resistance and diabetes [9, 10].

Chromium (Cr) was proposed to be an essential element about 50 years when its role was believed to be associated with glucose metabolism and insulin action. This role has recently been questioned as Cr has been proposed to act as a pharmacological agent [11, 12]. To achieve pharmacological effects, it is clear that supranutritional dose is necessary or subjects that carry risks for impaired glucose and/or lipid metabolism. Indeed, there is an interrelationship between chronic diseases and various micronutrients such as Cr, selenium (Se), and zinc (Zn) [13–16]. Significant alterations of these elements in diabetic individuals and animals have been attributed to insulin deficiency [13]. Patients with diabetes have lower serum Cr, Zn, and Se levels than healthy subjects [13]. Moreover, absorption and excretion of Cr are higher in diabetic subjects than in nondiabetic subjects [17, 18].

Various Cr chelates are available. The Cr histidinate (CrHis) complex is a form developed to enhance stability and absorption of Cr, which is shown in a human study [19]. The present study tested the hypothesis that CrHis is more efficacious than CrPic for improving glucose metabolism in diabetic subjects, with respect to the IκB/NF-κB pathway and Nrf2 responses in the brain. Inhibition of the IκB/NF-κB pathway or Nrf2 response may be involved in the amelioration of insulin resistance during chromium supplementation in the brain of diabetic rats [20]. Therefore, a combination of a high-fat diet (HFD) and low-dose streptozotocin (STZ) injection were used to create a type 2 diabetic animal model [16] to investigate the effect of CrHis/CrPic supplementation on changes in IκB/NF-κB pathway and Nrf2 expression in the brain under diabetic conditions.

Materials and Methods

Animals, Diets, and Experimental Design

Male Wistar rats (n=90, 8 weeks old) weighing 200–250 g were purchased from Firat University Laboratory Animal Research Centre (Elazig, Turkey) and reared at the temperature of 22±2 °C, humidity of 55±5 %, and with a 12/12-h light/dark cycle. The experiment was conducted under the protocol approved by the Ethical Committee of Firat University. All procedures involving rats were conducted in strict compliance with relevant laws, the Animal Welfare Act, Public Health Services Policy, and guidelines established by the Institutional Animal Care and Use Committee of the university. Rats consumed a standard diet and tap water ad libitum.

Ingredients and chemical composition of the basal (control) diet are shown in Table 1. The diets were stored at 4 °C cold chamber. Animals were fed with a diet consisting of either 8 % fat (control) or 40 % fat (HFD). CrPic and CrHis (Nutrition 21, Inc., Purchase, NY, USA) chelates were dissolved in water to assure daily consumption of 8 μg elemental Cr via drinking water for 12 weeks. This amount was calculated based on 560 μg Cr that is needed for a 70-kg adult human after adjusting doses based on metabolic body size ($70^{0.70}$=19.60 kg, needing 560 μg Cr; ~$0.250^{0.70}$= 0.38 kg needing 10.8 μg Cr).

A rat model of type 2 diabetes created by feeding with a HFD and STZ treatment developed by Reed et al. [21] provides a novel animal model for type 2 diabetes that is applicable in testing antidiabetic compounds. In this model, established hyperglycaemia status (glucose level >140 mg/dl) after STZ injection (40 mg/kg i.p., for 2 weeks) in high-fat fed rats was not due to a greater decline in β-cell function. Before STZ injection, glucose concentrations of rats were measured and compared to controls.

The 2×3 factorially arranged experimental groups were: group I (rats fed with the control diet only), group II (rats fed with the control diet and supplemented with CrPic), group

Table 1 Composition of experimental diets

Ingredients (g/kg)	Control diet	High-fat diet
Casein	200.0	200.0
Starch	615.0	145.0
Sucrose	–	150.0
Maize oil	80.0	–
Beef tallow	–	400.0
Cellulose	50.0	50.0
Vitamin–mineral premix[a]	50.0	50.0
DL-Methionine	3.0	3.0
Choline chloride	2.0	2.0

[a] The vitamin–mineral premix provides the following (per kilogram): all-*trans*-retinyl acetate, 1.8 mg; cholecalciferol, 0.025 mg; all-*rac*-a-tocopherol acetate, 12.5 mg; menadione (menadione sodium bisulfate), 1.1 mg; riboflavin, 4.4 mg; thiamine (thiamine mononitrate), 1.1 mg; vitamin B_6, 2.2 mg; niacin, 35 mg; Ca pantothenate, 10 mg; vitamin B_{12}, 0.02 mg; folic acid, 0.55 mg; *d*-biotin, 0.1 mg; manganese (from manganese oxide), 40 mg; iron (from iron sulfate), 12.5 mg; zinc (from zinc oxide), 25 mg; copper (from copper sulfate), 3.5 mg; iodine (from potassium iodide), 0.3 mg; selenium (from sodium selenite), 0.15 mg; choline chloride, 175 mg

III (rats fed with the control diet and supplemented with CrHis), group IV (diabetic rats fed with the HFD diet), group V (diabetic rats fed with the HFD diet and supplemented with CrPic), and group VI (diabetic rats fed with the HFD diet and supplemented with CrHis).

Western Blot Analyses

In all groups, brains were removed from sacrificed rats by cervical dislocation. Small pieces of samples in each group of animals were pooled together for Western blot analysis. Protein extraction was performed as follows: The sample was homogenized in an ice-cold 1 ml of hypotonic buffer A [10 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) (pH 7.8), 10 mM KCl, 2 mM MgCl2, 1 mM dithiothreitol (DTT), 0.1 mM ethylene diamine tetraacetic acid (EDTA), and 0.1 mM phenylmethylsulfonyl fluoride (PMSF)]. A solution of 80 μl of 10 % Nonidet P-40 (NP-40) was added to the homogenates, and the mixture was centrifuged for 2 min at 14,000×*g*. The supernatant was collected as a cytosolic fraction for nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor, alpha (IκBα) and 4-hydroxynonenal (4-HNE) assays. The precipitated nuclei were washed once with 500 μl of buffer A plus 40 μl of 10 % NP-40, centrifuged, resuspended in 200 μl of buffer C [50 mM HEPES (pH 7.8), 50 mM KCl, 300 mM NaCl, 0.1 mM EDTA), 1 mM DTT, 0.1 mM PMSF, and 20 % glycerol], and centrifuged for 5 min at 14,800×*g*. The supernatant containing nuclear proteins was collected for Nrf2 and NF-κB p65 [22].

Concentration of the protein was determined according to the procedure described by Lowry using a commercial protein assay kit (Sigma, St. Louis, MO, USA). Sodium dodecyl sulfate–polyacrylamide gel electrophoresis sample buffer containing 2 % β-mercaptoethanol was added to the supernatant. Equal amounts of protein (50 μg) were electrophoresed and subsequently transferred to nitrocellulose membranes (Schleicher and Schuell Inc., Keene, NH, USA). Nitrocellulose blots were washed twice for 5 min each in phosphate-buffered saline (PBS) and blocked with 1 % bovine serum albumin in PBS at room temperature for 1 h prior to application of the primary antibody. The antibody against Nrf-2 and 4-HNE adducts were the purchased from Santa Cruz Biotechnology, Inc. (Santa Cruz, CA, USA) and 4 Alpha Diagnostics (San Antonio, TX), respectively. Antibody against IκBα and NF-κB p65 was purchased from Abcam (Cambridge, UK). Primary antibody was diluted (1:1,000) in the same buffer containing 0.05 % Tween-20. The nitrocellulose membrane was incubated overnight at 4ºC with protein antibody. The blots were washed and incubated with horseradish peroxidase-conjugated goat anti-mouse IgG (Abcam, Cambridge, UK). Specific binding was detected using diaminobenzidine and H_2O_2 as substrates. Protein loading was controlled using a monoclonal mouse antibody against β-actin antibody (A5316; Sigma). Blots were performed at least three times to confirm data reproducibility. Bands were analyzed densitometrically using an image analysis system (Image J; National Institute of Health, Bethesda, USA).

Statistical Analysis

The data were analyzed using the general linear model procedure of SAS software [23]. The least square means of the groups were compared at a significant probability of less than 0.05 using ANOVA. Treatments were also compared using Student's unpaired *t* test for comparison of individual treatment. Between-group differences in latencies were analyzed by the analysis of variance for repeated measurements followed by Fisher's post hoc test for all groups.

Results

The brain NF-κB p65 subunit expression increased significantly in diabetic rats (Fig. 1a). Although Cr chelates did not alter brain NF-κB level in nondiabetic rats, both chelates significantly decreased brain NF-κB level in nondiabetic rats, at a greater extent in diabetic rats supplemented with CrHis than those supplemented with CrPic ($P<0.05$).

The diabetes decreased cerebral IκBα level (Fig. 1b). Despite no alteration in nondiabetic rats, Cr chelates increased cerebral IκBα level in diabetic rats. This increase was more in rats supplemented with CrHis than rats supplemented with CrPic, but did not reach level of nondiabetic rats.

The protein concentration of Nrf2 in the brain tissues for diabetic rats was lower than that for nondiabetic rats (Fig. 1c). Neither CrPic nor CrHis affected cerebral Nrf2 protein level in nondiabetic rats. The extent of protein level increase in diabetic rats supplemented with CrHis was greater than those supplemented with CrPic.

The brain 4-HNE protein adducts increased significantly in diabetic rats (Fig. 1d). Supplemental Cr chelates did not affect cerebral level of 4-HNE protein adducts. However, both Cr forms decreased the level of 4-HNE protein adducts in brains of diabetic rats at a similar extent.

Discussion

The purpose of this study was to determine the effects of CrHis or CrPic on inflammatory markers in the brain of diabetic rats. Similar to the present study, other reports have shown that

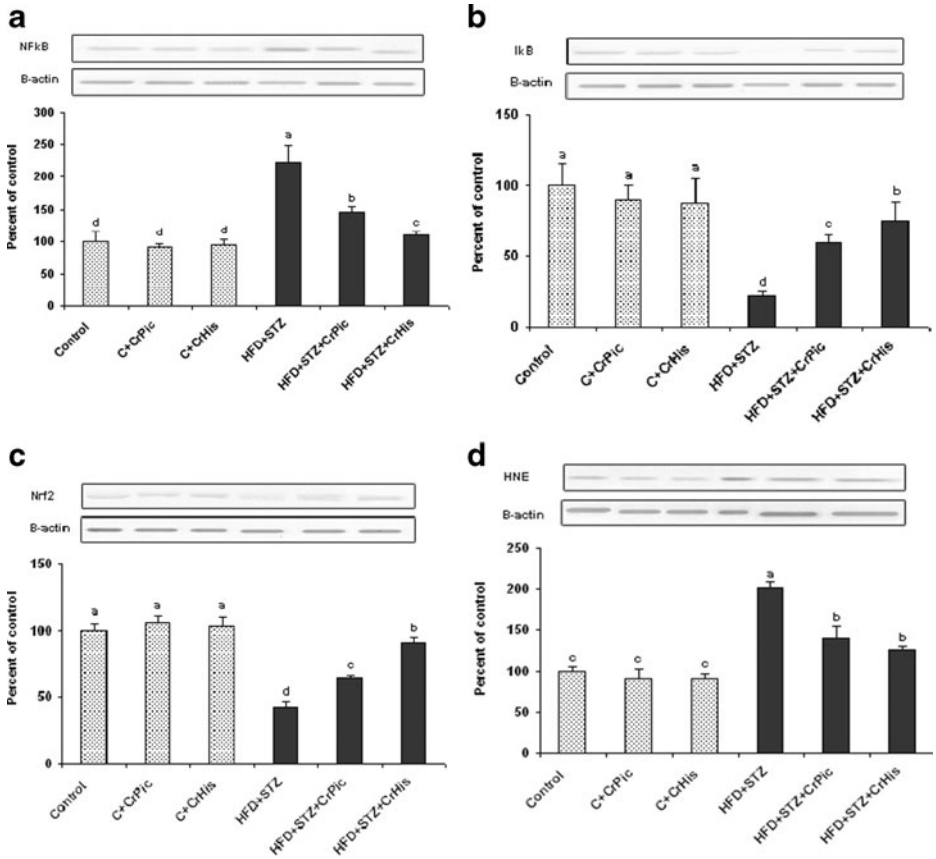

Fig. 1 Western blot analysis of cerebral nuclear factor-kappa B (*NF-κB p65*) (**a**), nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor (*IκBα*) (**b**), nuclear factor (erythroid-derived 2)-like 2 (*Nrf2*) (**c**), and 4-hydroxynonenal (*HNE*) protein adducts (**d**) in nondiabetic (fed control diet, *c*) and diabetic (injected with streptozotocin, STZ, and fed with high-fat diet, *HFD*) rats receiving 8 μg elemental Cr via drinking water in the form of chromium picolinate (*CrPic*) or chromium histidinate (*CrHis*). A representative blot is shown (n=3). Actin was included to ensure equal protein loading. Densitometric analyses of these bands are represented as percent of control. Values are means± standard error of the mean. *Different letters* indicate group mean differences

diabetes causes alterations in synthesis or concentrations of inflammatory cytokines [24–26]. In this experiment, CrHis or CrPic decreased NF-κB activation in rats with HFD/STZ-induced brain injury, suggesting that CrPic and CrHis decrease lipid peroxidation via the Nrf2/ARE-mediated pathway, as reflected by 4-HNE protein adducts. Jain et al. [25] reported that chromium niacinate supplementation lowered the blood levels of tumor necrosis-α (TNF-α), interleukin-6 (IL-6), C-reactive protein, and cholesterol and CrPic supplementation caused a decrease in TNF-α, IL-6, and lipid peroxidation in rats.

Various extracellular signals can initiate NF-κB pathways by activating IκB kinase complex (IKK). The activation of IκB kinase complex leads to the phosphorylation, ubiquitination, and degradation of IκB, which allows NF-κB to enter the nucleus where it regulates the expression of specific genes [4, 27]. Zhang et al. [28] hypothesized that IKKβ/NF-κB pathway is linked to dysfunction of hypothalamic signaling induced by overnutrtion. They [28] studied the connection between IKKβ/NF-κB and central dysregulation of energy balance (insulin/leptin pathway) in the hypothalamus and found that chronic high-fat feeding up-activated NF-κB in hypothalamus. In a previous study, we reported that NF-κB p65 increased in rats fed with HFD compared to rats fed with standard diet, but reduced by the CrHis administration [29].

Nrf2 is considered as the axis of defense against oxidative stress, and there is a clear correlation between pathogenesis of diabetic neuropathy and Nrf2 pathway [8, 10]. Nrf2 pathway has been implicated to play a significant role in contributing to the antioxidant defense of the body. Excess production of ROS is considered to cause abnormal axon morphology and altered neuronal membrane permeability along with causing functional modification of various cellular proteins [26, 30]. Nrf2 and HO-1 have been shown to possess protective effect against STZ-induced diabetes and diabetic neuropathy [8]. In the present work, Nrf2 level in the HFD/STZ-induced diabetes group was lower than those of controls in brain, whereas Cr treatment induced activation of Nrf2 and enhanced nuclear translocation and subsequent ARE binding, suggesting that Cr may be involved in stabilization and activation of Nrf2. Yet, this needs further studies to be substantiated. In a previous study, it was shown that hepatic Nrf2 and HO-1 levels increased by supplementation of CrHis in rats fed with HFD [29].

Oxidative stress plays a major role in diabetes as well as in diabetic neuropathy [31, 32]. The reaction of free radicals with membrane lipids causes the formation of lipid peroxidation products including several aldehydic compounds, one of which is highly toxic and called 4-HNE. This is frequently measured as an indicator of lipid peroxidation and oxidative stress in vivo and considered as an index of

oxidative stress. Moreover, it is one of the most effective activators of Nrf2 [33]. 4-HNE forms adducts with key neuronal proteins [34] and these adducts have been shown to be increased in the peripheral nerves of STZ diabetic rats [34, 35]. In the present study, 4-HNE protein adducts, indicator of lipid peroxidation, in the brain of diabetic rats decreased when dietary CrHis or CrPic was supplemented. CrHis supplementation did not alter these parameters in nondiabetic rats. The current study appears to be the first to examine the specific association between dietary Cr intake and 4-HNE protein adducts in diabetic rats. Significantly lower levels of 4-HNE adducts observed in diabetic rats may indicate an association between Cr intake and 4-HNE adducts for diabetic rats. Indeed, previous findings have shown that the production of 4-HNE is altered in diabetes, resulting in increased susceptibility of the tissues to injury [36]. Cr is postulated to function to augment antioxidant defense system, as confirmed by decreases in lipid peroxidation, TNF-α, and IL-6 [16, 25]. Preuss et al. [37] also reported a decrease in hepatic TBARS formation by supplementation of CrPic and Cr nicotinate in rats.

In conclusion, diabetes affected the IκB/NF-κB pathway and Nrf2 responses in brain tissue, as reflected by increased cerebral NF-κB and 4-HNE protein adducts levels and decreased cerebral Nrf2and IκBα. Cr chelates (CrPic and CrHis) exerted protective role in diabetic rats. Histidinate form of Cr was superior to picolinate form of Cr in reversing brain injury in diabetes, as reflected by a greater reduction in level of NF-κB and greater increases in levels of IκBα and Nrf2 in the brain.

Acknowledgments The authors thank Nutrition 21, Purchase, NY for providing financial support for this study.

Conflict of interest The study was funded by Nutrition 21, Inc., NY, USA. Nutrition 21 also supplied the chromium picolinate and chromium histidinate used in the study. James R. Komorowski is an employee of Nutrition 21, the distributors of chromium picolinate under a license from the USDA.

References

1. Feldman EL, Russell JW, Sullivan KA, Golovoy D (1999) New insights into the pathogenesis of diabetic neuropathy. Curr Opin Neurol 12:553–563
2. Biessels GJ, Kamal A, Urban IJ, Spruijt BM et al (1998) Water maze learning and hippocampal synaptic plasticity in streptozotocin diabetic rats: effects of insulin treatment. Brain Res 800:125–135
3. Vincent AM, Edwards JL, Sadidi M, Feldman EL (2008) The antioxidant response as a drug target in diabetic neuropathy. Curr Drug Targets 9:94–100
4. Kumar A, Negi G, Sharma SS (2011) JSH-23 targets nuclear factor-kappa B and reverses various deficits in experimental diabetic neuropathy: effect on neuroinflammation and antioxidant defence. Diabetes Obes Metab 13:750–758
5. Cameron NE, Cotter MA (2008) Pro-inflammatory mechanisms in diabetic neuropathy: focus on the nuclear factor kappa B pathway. Curr Drug Targets 9:94–100
6. Meunier A, Latrémolière A, Dominguez E et al (2007) Lentiviral-mediated targeted NF-kappaB blockade in dorsal spinal cord glia attenuates sciatic nerve injury-induced neuropathic pain in the rat. Mol Ther 15:687–697
7. Kim J, Cha YN, Surh YJ (2010) A protective role of nuclear factor-erythroid 2-related factor-2 (Nrf2) in inflammatory disorders. Mutat Res 690:12–23
8. Negi G, Kumar A, Joshi RP, Sharma SS (2011) Oxidative stress and Nrf2 in the pathophysiology of diabetic neuropathy: old perspective with a new angle. Biochem Biophys Res Commun 408:1–5
9. Yoh K, Hirayama A, Ishizaki K et al (2008) Hyperglycemia induces oxidative and nitrosative stress and increases renal functional impairment in Nrf2-deficient mice. Genes Cells 13:1159–1170
10. Negi G, Kumar A, Sharma SS (2011) Melatonin modulates neuroinflammation and oxidative stress in experimental diabetic neuropathy: effects on NF-kappaB and Nrf2 cascades. J Pineal Res 50:124–131
11. Vincent JB (2010) Chromium: celebrating 50 years as an essential element? Dalton Trans 39:3787–3794
12. Di Bona KR, Love S, Rhodes NR, McAdory D et al (2011) Chromium is not an essential trace element for mammals: effects of a "low-chromium" diet. J Biol Inorg Chem 16:381–390
13. Wallach S (1985) Clinical and biochemical aspects of chromium deficiency. J Am Coll Nutr 4:107–120
14. Faure P, Roussel A, Coudray C et al (1992) Zinc and insulin sensitivity. Biol Trace Elem Res 32:305–310
15. Becker DJ, Reul B, Ozcelikay AT et al (1996) Oral selenate improves glucose homeostasis and partly reverses abnormal expression of liver glycolytic and gluconeagenic enzymes in diabetic rats. Diabetologia 39:3–11
16. Sahin K, Onderci M, Tuzcu M et al (2007) Effect of chromium on carbohydrate and lipid metabolism in a rat model of type 2 diabetes mellitus: the fat-fed, streptozotocin-treated rat. Metabolism 56:1233–1240
17. Ding W, Chai Z, Duan P et al (1998) Serum and urine chromium concentrations in elderly diabetics. Biol Trace Elem Res 63:231–237
18. Cefalu WT, Wang ZQ, Zhang XH et al (2002) Oral chromium picolinate improves carbohydrate and lipid metabolism and enhances skeletal muscle Glut-4 translocation in obese, hyperinsulinemic (JCR-LA corpulent) rats. J Nutr 132:1107–1114
19. Anderson RA, Polansky MM, Bryden NA (2004) Stability and absorption of chromium and absorption of chromium histidinate complexes by humans. Biol Trace Elem Res 101:211–218
20. Häcker H, Karin M (2006) Regulation and function of IKK and IKK-related kinases. Sci STKE 2006(357):re13
21. Reed MJ, Meszaros K, Entes LJ (2000) A new rat model of type 2 diabetes: the fat-fed, streptozotocin-treated rat. Metabolism 49:1390–1394
22. Farombi EO, Shrotriya S, Na HK et al (2008) Curcumin attenuates dimethylnitrosamine-induced liver injury in rats through Nrf2-mediated induction of heme oxygenase-1. Food Chem Toxicol 46:1279–1287
23. SAS, User's Guide (2002) Statistics, version 9. Statistical Analysis System. SAS Inst., Inc., Cary, NC
24. Jain SK, Lim G (2006) Chromium chloride inhibits TNF-α and IL-6 secretion in isolated human blood monoclear cells exposed to high glucose. Horm Metab Res 38:60–62
25. Jain SK, Rains JL, Croad JL (2007) Effect of chromium niacinate and chromium picolinate supplementation on lipid peroxidation, TNF-a, IL-6, CRP, glycated hemoglobin, triglycerides and cholesterol levels in blood of streptozotocin-treated diabetic rats. Free Radic Biol Med 43:1124–1131

26. Figueroa-Romero C, Sadidi M, Feldman EL (2008) Mechanisms of disease: the oxidative stress theory of diabetic neuropathy. Rev Endocr Metab Disord 9:301–314
27. Acharyya S, Villalta SA, Bakkar N et al (2007) Interplay of IKK/NF-kappaB signaling in macrophages and myofibers promotes muscle degeneration in Duchenne muscular dystrophy. J Clin Invest 117:889–901
28. Zhang X, Zhang G, Zhang H et al (2008) Hypothalamic IKKbeta/NF-kappaB and ER stress link overnutrition to energy imbalance and obesity. Cell 135:61–73
29. Tuzcu M, Sahin N, Orhan C et al (2011) Impact of chromium histidinate on high fat diet induced obesity in rats. Nutr Metab (Lond) 3:8–28
30. Russell JW, Golovoy D, Vincent AM et al (2002) High glucose-induced oxidative stress and mitochondrial dysfunction in neurons. FASEB J 16:38–48
31. Sima AA, Sugimoto K (1999) Experimental diabetic neuropathy: an update. Diabetologia 42:773–788
32. Akude E, Zherebitskaya E, Roy Chowdhury SK et al (2010) 4-Hydroxy-2-nonenal induces mitochondrial dysfunction and aberrant axonal outgrowth in adult sensory neurons that mimics features of diabetic neuropathy. Neurotox Res 17:28–38
33. Ishii T, Itoh K, Ruiz E et al (2004) Role of nrf2 in the regulation of cd36 and stress protein expression in murine macrophages activation by oxidatively modified LDL and 4-hydroxynonenal. Circ Res 94:609–616
34. Obrosova IG, Drel VR, Pacher P et al (2005) Oxidative-nitrosative stress and poly (ADPribose) polymerase (PARP) activation in experimental diabetic neuropathy: the relation is revisited. Diabetes 54:3435–3441
35. Obrosova IG, Ilnytska O, Lyzogubov VV et al (2007) High-fat diet induced neuropathy of pre-diabetes and obesity: effects of "healthy" diet and aldose reductase inhibition. Diabetes 56:2598–2608
36. Praticò D, Tangirala RK, Rader DJ et al (1998) Vitamin E suppresses isoprostane generation in vivo and reduces atherosclerosis in Apo E-deficient mice. Nat Med 4:1189–1192
37. Preuss HG, Grojec PL, Lieberman S, Anderson RA (1997) Effects of different chromium compounds on blood pressure and lipid peroxidation in spontaneously hypertensive rats. Clin Nephrol 47:325–330