

THE EFFECT OF MICROELEMENTS SUPPLEMENTATION ON β -OXIDATION ACTIVITY IN HEALTHY AND TYPE 1 DIABETIC RATS

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SUMMARY

Diabetes mellitus type 1 disease changes the activity of fatty acid degradation as compared to healthy animals. Supplementation *in vitro* with microelements chromium Cr³⁺ and selenium Se⁴⁺ and Se²⁻ in non-toxic (96.15 μ mol (5 ppm) for chromium and 6.33 μ mol (0.5 ppm) for selenium) concentrations strongly stimulates the activity of this process in diabetic rats. In healthy animals only chromium Cr³⁺ in concentration of 96.15 μ mol (5 ppm) stimulated β -oxidation activity in lymphocytes. It may indicate the beneficial effect of supplementation of the diet with microelements, chromium Cr³⁺ and selenium Se⁴⁺ or Se²⁻ at concentrations as low as 100 μ mol for chromium and 6 μ mol for selenium, respectively.

Key words: microelements, type 1 *diabetes mellitus*, rats, β -oxidation

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INTRODUCTION

Diabetes mellitus is one of the most important metabolic diseases in humans and animals. There are recognized two distinct form of this disease: type 1 (insulin dependent) and type 2 (insulin independent) form. Type 1 diabetes mellitus is the effect of insulin deficiency as the result of destruction of pancreatic B cells. Insulin injections restore the sugars utilization to the level comparable to those in healthy organisms. In type 2 diabetes mellitus insulin therapy is ineffective because of receptors abnormality, signaling defects. However, in some patient's identification of such changes is not possible. Insulin is responsible for entry of glucose into cells of muscle, adipose and other tissues, stimulation of storage of glucose in the form of glycogen in the liver and decreasing the glucose concentration in the blood. Insulin promotes the synthesis of fatty acids in the liver, which are used for synthesis of triacylglycerols, and has fat-sparing effect by preferential oxidation of sugars instead of fatty acids for energy production. In diabetic organisms metabolism of sugars is very limited. This energy source must be substituted by other group of compounds. In diabetes when insulin level is very low, lipolytic processes are not suppressed by this hormone, triacylglycerols from fat tissue are decomposed to glycerol and free fatty acids, which are metabolized to acetyl-Co-A, the substrate for Krebs' cycle, and ketone bodies, acetoacetate and β -hydroxyl-butyrate. These compounds in diabetic organisms are partially metabolized to acetone.

Chromium ions (III) are recognized as a factor increasing glucose uptake in cells (1, 2). Important is the form of chromium compound. Hinigner et al. (3) reported, that chromium (III) had no toxic effect on DNA of human keratinocytes at concentrations of 250 μ mol for CrCl and Cr-histidinate, as well as 120 μ mol for chromium picolinate (saturating concentration). Chromium

picolinate supplementation (80 μ g per kilogram BW) resulted in diabetic rats in lowering of glucose level by 63% ($p < 0.001$), total cholesterol by 9.7% ($p < 0.001$) and triacylglycerols by 6.6% ($p < 0.001$) (4). Jain et al. (5) showed, that chromium picolinate, as well as chromium niacinate (400 μ g per kilogram BW) lowered not only triacylglycerols and cholesterol levels ($p = 0.04$) but also TNF- α ($p = 0.04$), IL-6 ($p = 0.02$), C-reactive peptide ($p = 0.02$) and lipids peroxidation ($p = 0.01$), which are increased in streptozotocin-induced diabetic rats. Chromium (VI) is recognized to be toxic for cells during reduction from Cr⁶⁺ to Cr³⁺ forming free reactive oxygen species (ROS) as intermediates (6, 7).

Selenium deficiency in humans manifests as Keshan disease, Kashin-Back disease and several kind of myopathies (8), what may suggest the potential participation of this ion in regulation of energy production processes. The reason of these pathologies is very low selenium level in the soil resulting in very low content of this essential trace element in food. The biologically active forms of selenium in organisms are glutathione peroxidase, 5'-iodotyrosine deiodase, thioredoxine reductase and seleno-protein P (9). Results of animal studies suggest that dietary selenium from inorganic or organic sources was toxic at concentrations exceeding 5 ppm (63.3 μ mol). Increasing degree of toxicity of this essential element was estimated as follows: seleniferous grains > selenates > selenites > selenides and elemental selenium. Selenium intake recommendations are well known but the form of this supplementation is not taken into account. However, metabolic effects of various selenium oxidation state and compounds are often quite different. In plant fertilization inorganic forms are used – sodium selenite and/or sodium selenate mainly as additives of microelement fertilizers applied on leaves or directly to the soil (10). In organisms selenium is mostly present in the organic form of seleno-methionine and/or seleno-cysteine.

We reported the action of chromium Cr^{3+} , selenium Se^{4+} and Se^{2-} ions on glucose uptake and fatty acids degradation in healthy rats (11). The aim of presented studies was to study the effect of these ions, as well as L-carnitine supplementation on β -oxidation of fatty acids in healthy rats and rats with experimental diabetes mellitus type 1.

MATERIALS AND METHODS

Animals: 14 male adult Wistar rats weighing 130–150 g were randomly divided into 2 groups of 7 rats each. Experimental animals were injected intraperitoneally with streptozotocin (50 mg/kg body weight). All animals (healthy and diabetic) received a standard diet (AIN-93) having free access to food and drinking water. At the end of the experimental period, the animals were anesthetized by intraperitoneal injection of thiopental and blood was collected by heart puncture into the plastic tubes containing EDTA as an anticoagulant.

Methods: β -oxidation activity of fatty acids was estimated according to Manning et al (12) in isolated lymphocytes in own modification (13). Lymphocytes were isolated by centrifugation on HISTOPAQUE-1077 (Sigma), resuspended in phosphate buffered saline (PBS) (calcium and magnesium free) up to a final concentration of approximately 1 mg/ml of protein. Lymphocytes (25–50 μg of protein) were incubated in a final volume of 200 μl in triplicates for 60 minutes at 37 $^{\circ}\text{C}$ in the presence of 50 μmol palmitic acid in Hank's balanced salt solution (HBSS) supplemented with 1 $\text{mg} \cdot \text{ml}^{-1}$ of fatty acids free bovine serum albumin (BSA) and 0.1 $\mu\text{Ci/ml}$ of [9,10]- ^3H -palmitic acid (Amersham). The reaction was terminated by the addition of 200 μl of 10% trichloroacetic acid (TCA) and 100 μl of HBSS. Precipitated fatty acid and protein were separated by centrifugation for 10 min at 3,000 rpm and supernatant was collected and alkalized with 100 μl of 2 mol NaOH. The amount of liberated tritiated water, separated from remaining radioactive substrate on anion exchange column (0,5 x 2 cm) (Bio-Rad AG 1X-8), depended on the activity of palmitic acid degradation, which was expressed as pmols of decomposed palmitic acid per 1 min \cdot 1 mg^{-1} of lymphocytes protein.

Incubation media were supplemented with chromium ions (Cr^{3+}) in the form of chromium acetate, selenium ions (Se^{4+}) in the form of sodium selenite and selenium ions (Se^{2-}) in the form of seleno-L-methionine. Concentrations used were 96.15 μmol (5 ppm) for chromium and 6.33 μmol (0.5 ppm) for selenium ions. These concentrations are commonly recognized as non-toxic for animals.

Statistical analysis: The data are presented as the mean \pm SD of 7 experiments. Statistical differences between samples were calculated by Duncan test and t-test.

RESULTS AND DISCUSSION

The effect of microelements on fatty acids degradation was examined in healthy animals and in animals one week after injection with streptozotocin.

The effects on diabetes type 1 in rats injected with streptozotocin are shown in Table 1.

Table 1. The effect of streptozotocin injection on body weight gain and biochemical parameters of blood ($n = 7$; Mean \pm S.D.)

Parameter		Healthy	Diabetic
Streptozotocin treated	$\text{mg} \cdot \text{kg}^{-1}$ b.w.	0	51.70 ± 1.67
Body weight gain	g per week	55.00 ± 3.21	$35.50 \pm 4.66^*$
Insulin conc.	$\text{pmol} \cdot \text{dm}^{-3}$	552.10 ± 174.70	$46.37 \pm 17.67^*$
Glucose conc.	$\text{mmol} \cdot \text{dm}^{-3}$	5.34 ± 0.54	$28.74 \pm 4.05^*$

* Differences in are statistically significant at $p = 0.001$.

The used dose of streptozotocin caused drop of insulin from 552.10 ± 174.70 to 46.37 ± 17.67 $\text{pmols} \cdot \text{dm}^{-3}$ and increase of glucose level from 5.34 ± 0.54 to 28.74 ± 4.05 $\text{mmol} \cdot \text{dm}^{-3}$ in the blood of healthy and diabetic animals, respectively. The body weight gain after 7 days was 55.0 ± 3.21 g for healthy Wistar rats as compared to 33.5 ± 4.66 g for diabetic ones. Such animals were used for studies of the activity of β -oxidation of fatty acids.

The results of degradation of fatty acids by lymphocytes from healthy and diabetic rats after supplementation with ions of trace elements are presented in Table 2.

Table 2. The effect of chromium Cr^{3+} ions (96.15 mmol), selenium Se^{4+} and selenium Se^{2-} ions (6.33 mmol) on fatty acids degradation in lymphocytes isolated from healthy and type 1 diabetic Wistar rats ($n = 7$).

Media enrichment	β -oxidation activity $\text{pmol/min} \cdot \text{mg}$ of protein (mean \pm S.D.)		
	Healthy	Diabetic	Statistical Sig. P
Control	27.46 ± 0.68^d	24.80 ± 2.02^a	0.004
+ Cr^{3+}	45.02 ± 1.10^e	54.43 ± 3.93^c	< 0.0001
+ Se^{4+}	28.11 ± 1.44^d	39.81 ± 2.21^b	< 0.0001
+ Cr^{3+} , + Se^{4+}	22.84 ± 0.64^a	33.41 ± 2.07^{ab}	< 0.0001
+ Se^{2-}	26.51 ± 0.75^{cd}	37.61 ± 2.76^{ab}	< 0.0001
+ Cr^{3+} , + Se^{2-}	24.78 ± 1.46^b	35.03 ± 2.74^b	< 0.0001

Means \pm S.D.

(X) ^{a-e} – Means in column not sharing the same superscript letter are significantly different ($p < 0.05$)

These data indicated, that in controls in diabetic rats the activity of fatty acid degradation was slightly lower as compared to the controls of healthy animals (24.80 ± 0.72 and 27.46 ± 0.20 $\text{pmol} \cdot \text{min}^{-1} \cdot \text{mg}^{-1}$ of protein). This difference is statistically highly significant ($p < 0.001$). Chromium Cr^{3+} ions are recognized as a very strong activators of glucose metabolism (14, 15) and β -oxidation process (16, 17) in healthy objects. Similar effect on the degradation of lipids may be observed when analyzing results of Brighenti et al. (18) and Letexier et al. (19) in volunteers fed with energy restricted diet. Increased activity of β -oxidation was also observed in healthy rats on the diet with non-digestible oligofructans substituted for starch (20, 21). The effect of chromium ions was proportional to chromium and fibrous oligosugars concentration and was almost 2-times higher in experimental animals as compared to controls. The rate of activation of fatty acids decomposition is more effective in diabetic rats as compared to healthy ones (54.43 ± 1.39 and 45.02 ± 0.33 , respectively). Most probably it is

caused by the loss of inhibitory effect of insulin, which is absent in diabetic objects (22). In healthy rats only the stimulatory effect of chromium Cr^{3+} was observed. One of the possible explanation of these observations might be the bioavailability of selenium ions, especially when in concentrations as low as $6.33 \mu\text{mol}$ are accessible (23). All other combinations of ions were ineffective in modulation of the activity of fatty acids decomposition in healthy rats. On the other hand, in diabetic animals all variants of supplementation increased the activity of β -oxidation. However, the stimulatory effect was not as high as this observed for chromium alone. Additionally, fatty acids degradation was better stimulated by selenium Se^{4+} and Se^{2-} ions when used alone (39.81 ± 2.21 and $37.61 \pm 2.76 \text{ pmol} \cdot \text{min}^{-1} \cdot \text{mg}^{-1}$ of protein, respectively) than in combination with chromium Cr^{3+} . Combinations of chromium with selenium were not as effective as selenium Se^{4+} and Se^{2-} in stimulation of β -oxidation in lymphocytes isolated from the blood of diabetic rats (33.41 ± 2.07 and $35.03 \pm 2.74 \text{ pmol} \cdot \text{min}^{-1} \cdot \text{mg}^{-1}$ of protein, respectively).

The results of the activity of β -oxidation presented as change in percent of control (Fig. 1) showed, that in healthy animals only chromium Cr^{3+} was effective as a stimulator of fatty acids degradation, however, in type 1 diabetic animals all ions of trace elements used separately were strong activators of this process. The most efficient was chromium (III) (120% of stimulation as compared to control). Less effective were ions of selenium (IV) – 60% of stimulation and selenium (II) – 50% of stimulation. Simultaneous supplementation with chromium and selenium ions resulted in lower effectiveness as compared to variant contained individual ions.

In animal system selenium supplementation (selenium yeast) improve glucose levels (24) in diabetic hamster as well as the form of diphenyl diselenide exhibits beneficial effects against the development of diabetes in rats (25). Studies in humans are complicated because of commonly used supplementation with multivitamin and multiminerals supplements (26, 27, 28). In the case of chromium the effects of these trace elements are still discussed. Kleefstra et al. (29) reported that there is no evidence in improving glycemic control by chromium yeast, while Lai et al. (30) described beneficial action of this chromium prepara-

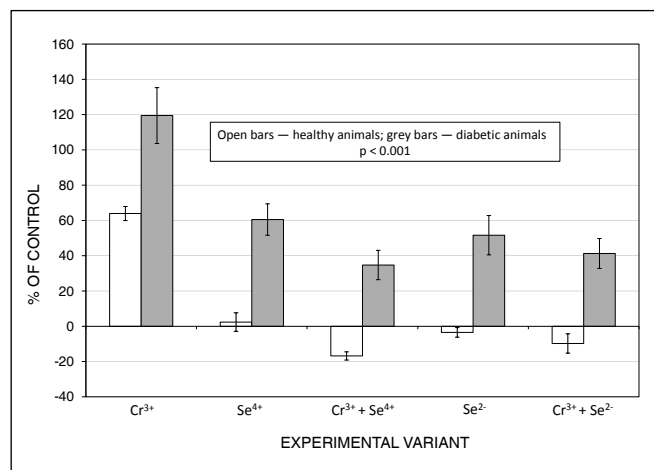


Fig. 1. Comparison of the efficiency of β -oxidation (expressed as change in percent of control) in lymphocytes from healthy and type 1 diabetic rats. Incubation mixtures were supplemented with Cr^{3+} ions ($96.15 \mu\text{mol}$), Se^{4+} and Se^{2-} ions ($6.33 \mu\text{mol}$) (mean \pm S.D.; $n = 7$).

tion on carbohydrate and lipid metabolism. Differences between these studies were only in studied subjects – diabetic humans in Kleefstra's experiments and rats in Lai. The data presented by Kleefstra et al. (29) are questioned by a number of authors who found positive changes in carbohydrate and lipids metabolism after supplementation with other than chromium yeast supplements: chromium picolinate (4, 31), chromium niacinate (5) or chromium-(D-phenylalanine) (32). Chromium ions improved lipids metabolism lowering LDL/HDL ratio and triacylglycerols concentration. These observations should be, in part, the effect of stimulation of fatty acids degradation as presented in this paper.

CONCLUSIONS

1. Chromium and selenium ions are very effective stimulators of fatty acids degradation.
2. Selenium ions (Se^{4+} as well as Se^{2-}) are less effective in stimulation of β -oxidation as compared to chromium Cr^{3+} , especially in combination with chromium ions.
3. Combination of ions of microelements – chromium (Cr^{3+}) and selenium (Se^{4+}) and selenium (Se^{2-}) is beneficial for energy production in type-1 diabetic rats.

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TARGETED ACTION ON HIV AND TUBERCULOSIS NEEDED TO REACH DRUG USERS

cont. from p. 204

HIV weakens a person's immune system. Because of this, people living with HIV are up to 50 times more likely to develop TB in their lifetimes than people who are HIV negative. Without proper treatment, the majority of people living with HIV die within two to three months of becoming sick with TB. In 2006, 231,000 people died with HIV and TB. Many of these deaths were preventable.

Unsafe injecting drug use is now a major route of transmission for HIV. Excluding Africa, nearly one in three of all new HIV infections are attributable to unsafe injecting drug use. In areas of eastern Europe and central Asia, that figure rises to two out three new infections. In some areas of eastern Europe a significant association between HIV and multidrug-resistant TB has been observed by researchers.

Addressing TB/HIV is a key theme of the 2008 International AIDS Society conference and comes two months after world leaders issued a call to drastically cut the number of TB/HIV deaths by 2015 at the landmark Global Leaders' Forum on the co-epidemic, held at the UN headquarters in New York.

Joint Planning:

1. Multisectoral coordination on TB and HIV activities for drug users
2. National plans with roles and responsibilities of service providers
3. Staff training to build effective teams

4. Operational research on TB/HIV services for drug users

Key Interventions:

5. TB infection control in congregate settings including prisons
6. Case-finding protocol for TB and HIV for services dealing with drug users
7. Access to appropriate treatments for drug users
8. Isoniazid preventive therapy for drug users living with HIV
9. Health workers to assess and provide HIV prevention methods

Overcoming Barriers:

10. Universal access to TB and HIV prevention, treatment and care as well as drug treatment services to drug users
11. Quality medical services available to prisoners
12. Treatment adherence support measures for drug users
13. Other infections (e.g. hepatitis) and factors should not prevent drug users accessing HIV and TB treatments

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Note for the media WHO/8

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