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CHANGES OF BLOOD PARAMETERS ASSOCIATED WITH NICKEL ADMINISTRATION IN RATS

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Abstract

The aim of this work was to analyze the biochemical parameters of blood plasma in rats after intraperitoneal and peroral administration of nickel. Experimental group E1 was administered by nickel at a dose of 15 mg/kg, group E2 with 25 mg/kg and the group E3 with 35 mg/kg b.w. intraperitoneally (i.p.). After 48 hours, the blood samples were collected for biochemical analysis. Group E4 was dosed with nickel at a concentration of 100 mg/L in drinking water for 90 days. The parameters of mineral profile (Ca, P, Mg, Na, K and chlorides) and other parameters of energy, nitrogen and enzymatic profile (glucose, cholesterol, total proteins, triglycerides, urea, bilirubine, AST, ALT, ALP, GLDH) were measured. The most affected elements were potassium and calcium. Calcium concentration decreased significantly in group E1, E3 (P<0.05) and E4 (P<0.01). Concentrations of potassium decreased significantly in groups E1, E2 and E3 (P<0.05) and E4 (P<0.01). Mg concentration decreased in group E2 and E4 (P<0.05) and chlorides decreased only in i.p. groups E1 (P<0.05) and E3 (P<0.01). Analysis of nitrogen and energy profile showed a significant increase in concentrations of urea (group E1, P<0.05 and group E3, P<0.01), glucose (groups E2, E3, E4, P<0.05), and decrease in total proteins (group E1, P<0.01 and group E4, P<0.01), cholesterol (groups E2 and E4, P<0.05), bilirubine (all experimental groups, P<0.05) and triglycerides (group E1, E3, P<0.05 and group E2, P<0.01). Changes in enzymatic activity were as follows: activity increased in AST (group E3, P<0.05), ALT (group E1, P<0.05 and group E3, P<0.01), ALP (group E1, P<0.01 and groups E2, E3, E4, P<0.05), and GLDH (group E4, P<0.05). The results showed that nickel may have negative effects on the metabolism due to the disruption of certain metabolic processes. Decreased concentrations of mineral elements along with the parameters of energy and nitrogen profile suggest the renal dysfunction. Influence of enzymatic activity is sign of hepatocellular injury and liver functions. Nickel is capable to affect the metabolic processes and organ functions after an intraperitoneal and also peroral exposure.

Keywords: nickel, blood serum, biochemical profile, rat

Introduction

Nickel (Ni) is the 24th most abundant element and the earth's core is composed of 6 % of this metal. It is used in stainless steel products, nickel plating, to color ceramics, in batteries and other industrial applications (ATSDR, 2005). Anke *et al.* (1984) discussed the nickel essentiality for living systems and stated that low nickel offers reduce growth particularly during an intra-uterine development. Nickel deficiency is accompanied by histological and biochemical changes and reduced iron resorption and leads to anaemia. Nickel therefore performs a vital function in metabolism. However, the increasing utilization of heavy metals in modern industries leads to an increase in the environmental burden.

Nickel represents a good example of a metal whose use is widening in modern technologies. Its accumulation in the environment may represent a serious hazard to human health. Food is the major source of exposure to nickel but only about 1% is absorbed after the nickel intake in food. A human study shows that 40 more nickel was absorbed from the gastrointestinal tract when NiSO₄ (nickel sulphate) was given in the drinking water than when it was given in food (Sunderman *et al.*, 1989). When administered in water, significant elevations in nickel levels were found in the small intestine of mouse after 8 weeks of exposure. In

the kidneys, the nickel levels were only significantly higher than controls after 20 weeks of administration (Radike *et al.*, 2002). Skin allergies, lung fibrosis, kidney diseases, cardiovascular system damage, hematopoiesis disorder and stimulation of neoplastic transformation are the well-known health effects of nickel (Denkhaus and Salnikow, 2002, Oller *et al.*, 2008, Hfaiedh *et al.*, 2008, Adjroud and Mouffok, 2009, Adjroud, 2013).

Nickel compounds have been implicated in the etiology of human lung cancer. They activate hypoxia signaling pathways. The mechanism of this effect involves the ability of either soluble or insoluble nickel compounds to block iron uptake leading to cellular iron depletion or/and directly affect iron containing enzymes. This can lead to activation of hypoxic signaling (Costa *et al.*, 2005). The relative carcinogenic activity of nickel compounds is related to their water solubility (Coogan *et al.*, 1989). One of the major intracellular targets of nickel ions in the cell is the iron- and 2-oxoglutarate-dependent dioxygenase family of enzymes (Chervona *et al.*, 2012).

Nickel chloride also acts on cellular metabolism and in particular on erythrocyte glutathione peroxidase with consequent increase in oxidative stress. A significant decrease in intracellular glutathione in both human (25%) and fish erythrocytes (18%) after treatment with nickel chloride has been reported (De Luca *et al.*, 2007). Alteration in blood biochemistry caused by nickel peroral exposure was found in hens. Associations between nickel and calcium, magnesium, triglycerides and alanine transaminase (ALT) in blood serum were recorded (Kolesarova *et al.*, 2008a). Ni induced liver damage was clearly shown by the increased activities of serum hepatic enzymes along with increased elevation of lipid peroxidation indices. The toxic effect of Ni was also indicated by significantly decreased levels of enzymatic antioxidants superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione S-transferase (GST) and non-enzymatic antioxidants (glutathione, vitamin C and vitamin E) (Pari and Prasath, 2008). The nickel related changes in liver and also kidney functions were observed in nickel deficient animals. The activity of SDH and ALD, as well as the level of urea-N was significantly lower in the serum of Ni-deficient animals than in the control. Ni-deficient animals also had significantly lower enzyme activities in the heart (succinate dehydrogenase - SDH, hydroxybutyrate dehydrogenase - HBDH, aspartate aminotransferase - AST, ALT, aldolase - ALD and creatine kinase - CK), liver (sorbitol dehydrogenase - SDH and cholinesterase - CHE) and kidneys (HBDH and CK) (Szilágyi *et al.*, 1991). However, Kolesarova *et al.* (2008b) were no table to find the significant correlations between levels of nickel in internal organs and biochemical parameters.

The aim of this study was to determine the effect of intraperitoneal and peroral nickel exposure on the biochemical parameters in Wistar rats.

Materials and Methods

Fifty males Wistar rats were divided to 5 groups: nickel-treated groups (E1, E2, E3, E4) and control group (C), each containing 10 males. The males were housed individually in a plastic cages. The animals had unlimited access to drinking water and feed. The rats in the nickel (NiCl₂, Sigma, MO, USA) exposed groups were intraperitoneally dosed with 15 mgNi/kg b.w. (E1), 25 mgNi/kg b.w. (E2), 35 mgNi/kg b.w. (E3), and perorally at the concentration of 100 mg/L (E4) in drinking water for 90 days. Ten males (group C) served as the untreated control group without nickel treatment.

48 hours after an intraperitoneal administration of nickel (groups E1, E2, E3) and 90 days after the nickel intake in group E4, the rats were euthanized and blood samples were collected by cardiac puncture in glass tubes with heparin for analyses. The blood serum was separated by centrifugation at 3000 rpm for 30 minutes and stored at -18°C. The parameters of mineral profile (calcium, phosphorus, magnesium, sodium, potassium and chlorides) and other parameters of energy, nitrogen and enzymatic profile (glucose, cholesterol, total proteins, triglycerides, urea, bilirubine, aspartate aminotransferase – AST, alanine aminotransferase – ALT, alkaline phosphatase – ALP, glutamate dehydrogenase – GLDH) were measured by automatic analyzer Microlab 300 (Vital Scientific, Dieren, Netherland) and analyzer EasyLite (Medica, Bedford,

USA). The statistical analysis of variance and t-test were calculated using the Microsoft Excel software (Microsoft, USA).

Results and discussion

Nickel is known due its effects on haematological parameters leading to anaemia. Also it acts on metabolism and decreases the erythrocyte glutathione peroxidase with consequent increase in oxidative stress in human and fish (*De Luca et al.*, 2007). In this work, the biochemical parameters of blood serum were analyzed. The average concentrations and activities of biochemical parameters measured in rat blood serum are shown in *table 1 – 3*. The most affected elements were potassium and calcium. Potassium concentration significantly decreased in all experimental groups regardless of way of administration. The most significant decline ($P < 0.01$) was observed after a peroral intake of nickel during 90 days of experiment. Calcium concentrations also significantly decreased in group E1, E3 and E4 and the most significant change was again found in peroral group (2,16 mmol/L compared with the control 3.00 mmol/L). Significant decreases in calcium concentration were observed after nickel chloride administration in hens in dose of 2.0 mg/L of drinking water (*Kolesarova et al.*, 2008a). *Hayashi et al.* (2003) suggested that the increased excretion level of Ca is the result of renal dysfunction. The similar effect was described after peroral administration of cadmium during 3 months in pheasants (*Toman et al.*, 2006). However, *Kalafova et al.* (2010) were not able to find the significant changes in the serum concentrations of calcium in rabbits after nickel administration (17.5 and 35 mg/kg) for 30-90 days. On the contrary, *Hirano et al.* (1994) found increase in calcium concentration in blood serum in rats. Authors exposed the animals with NiSO_4 via inhalation. Phosphorus is present in blood serum mainly in form of inorganic phosphate, which is easy utilized in the chemical reactions. In our experiments, slight decrease in P concentrations was observed but the differences between control and experimental groups were not significant. Similarly, the sodium concentrations did not change significantly. Magnesium concentration in blood plasma decreased significantly in group E2 (25 g NiCl_2/kg i.p.) and E4 (100 mg NiCl_2/L p.o.). In experiment with hens, *Kolesarova et al.* (2008a) were not able to find any significant changes, even if the Mg concentration decreased.

Another significantly affected element in our experiment was potassium. It decreased in all experimental groups significantly. Significant depression of potassium in liver following nickel treatment in rats observed *Sidhu et al.* (2004). Changes in potassium blood levels may negatively affect the blood pressure as reviewed by *Haddy et al.* (2006). The higher decrease in K concentration was observed in peroral group (E4), so we can conclude that nickel may be an effective element in potassium decrease in blood after long-term intake. Potassium depletion can affect renal tubular cell function. Chronic potassium depletion can also cause a form of nephropathy known as hypokalaemic nephropathy, in which hypokalaemia itself is believed to cause a proximal tubular lesion associated with interstitial inflammation and fibrosis, leading to a fall in glomerular filtration rate (*Walsh et al.*, 2011). Chlorides play a major role in maintaining the pH levels of the body and also in metabolism to produce energy. Low plasma chloride levels are indicative of a lack of oxygen in the body or respiratory and metabolic acidosis. Hypochloridemia was found as most common chloride concentration change in stroke (*Alam et al.*, 2012). In our experiments, chloride concentrations decreased significantly in group dosed with 15 and 35 mgNi/kg (95.32 and 94.34 mmol/L, respectively) when compared to the control value (100.33 mmol/L). Kidney and liver failure disturbs the metabolism of many compounds like minerals, nutrients and enzymes. It leads to changes in the blood plasma constituents. The changes in plasma mineral elements in our experiments suggest the kidney function failure.

Table 1:

Mineral profile of the control and experimental rats

Element	Group (x±SD)				
	Control (n=10)	E1 – 15 mg/kg (n=10)	E2 – 25 mg/kg (n=10)	E3 – 35 mg/kg (n=10)	E4 – 100 mg/L (n=10)
Ca (mmol/L)	3.00±0.35	2.48±0.28*	3.21±0.47	2.42±0.23*	2.16±0.18**
P (mmol/L)	3.97±0.98	2.94±0.40	2.63±0.19	3.36±0.49	2.70±0.26
Mg (mmol/L)	1.57±0.50	1.25±0.26	0.88±0.23*	1.55±0.08	1.03±0.09*
Na (mmol/L)	140.9±1.60	141.20±2.55	141.29±1.82	141.41±3.69	140.95±2.74
K (mmol/L)	6.72±0.74	5.32±0.82*	5.48±0.61*	5.27±0.26*	4.93±0.45**
Cl ⁻ (mmol/L)	100.33±1.74	95.32±3.09*	100.12±4.46	94.34±2.67**	98.76±2.54

x = mean, SD = standard deviation, * = P<0.05, ** = P<0.01

A significant increase in urea concentration is evident after an intraperitoneal administration of nickel but not after a peroral exposure (Table 2). The mean concentration of urea increased from the control level 8.05 mmol/L to 24.10 mmol/L in group E3 (P<0.01). Urea is synthesized in the liver from ammonia, which is in turn generated as a break down product of ingested and endogenous protein. It is completely filtered by the kidney, but is also reabsorbed. Tubular reabsorption of urea is increased when tubular flow rates and volumes are decreased. Increases in serum urea may signal the onset of renal disease which has been shown in many other studies (Prabu *et al.*, 2010, Zaki and Mohamed, 2012). Nickel increases the protein catabolism. The total plasma proteins decreased significantly in the lowest-dose intraperitoneally exposed group E1 and in perorally exposed group E4 from the control 77.67 g/L to 69.97 and 65.45 g/L, respectively. Decreases in total plasma proteins are indicative of edema. It causes fluids to leave the circulatory system and localize in tissue spaces. Blood urea concentration reflects the balance between protein catabolism and clearance (Kemp *et al.*, 2001). Effect of nickel on the glucose metabolism is known (Clary, 1975, Chaudhry and Nath, 1984). In our study, the concentration of glucose increased significantly (P<0.05) in two high-dose groups E2 and E3, as well in peroral group E4 from the control 8.33 mmol/L to 9.26; 10.99 and 10.95 mmol/L, respectively. No significant changes in serum glucose concentration were found after nickel administration in fish (Ptashynski *et al.*, 2002), goats (Yousuf, 2002) and hens (Kolesarova *et al.*, 2008a). Total cholesterol and triglycerides showed decrease in mean concentration. Cholesterol decreased in group E2 and E4 from the control 2.80 mmol/L to 1.62 and 1.63 mmol/L, respectively. It means that both intraperitoneal and peroral administration of nickel affected the cholesterol concentration in blood serum. Our results do not correspond with those observed by Das *et al.* (2006). Authors found increase in total cholesterol and triglycerides after an intraperitoneal administration of nickel sulphate (2.0 mg/100 g b.w.) in rats. Lind *et al.* (2012) confirmed the relationship between nickel exposure and cholesterol and triglycerides in blood of old humans. Decrease in cholesterol concentrations in broiler chicken after addition of 50 mgNi/kg to feed mixture but no changes in cholesterol and increase in triglycerides concentrations were found in rabbits after the dose of 50 and 500 mgNi/kg in feed (Bersényi *et al.*, 2004). The bilirubine formed from breakdown of red blood cells is transported in plasma bound to albumin, so the decrease in bilirubine level is a result of reduction in the natural breakdown of red blood cells (Ogbe *et al.*, 2012). It therefore seems that nickel might provide protection to oxidative breakdown of red blood cells membranes.

Table 2:

Energy and nitrogen profile of the control and experimental rats

Parameter	Group (x±SD)				
	Control (n=10)	E1 – 15 mg/kg (n=10)	E2 – 25 mg/kg (n=10)	E3 – 35 mg/kg (n=10)	E4 – 100 mg/L (n=10)
urea (mmol/L)	8.05±0.97	13.32±5.40*	10.65±3.45	24.10±5.16**	7.01±1.13
TP (g/L)	77.67±5.48	69.97±2.27*	75.47±1.94	74.27±5.65	65.45±3.73**
Glu (mmol/L)	8.33±1.95	10.54±3.37	9.26±1.88*	10.99±1.99*	10.95±2.06*
Chol (mmol/L)	2.80±0.69	2.36±0.25	1.62±0.34*	2.80±0.07	1.63±0.15*
Bil (mmol/L)	57.90±26.52	16.18±4.68*	15.67±6.24*	25.16±3.16*	14.37±4.28*
TG (mmol/L)	1.78±0.43	1.18±0.30*	0.75±0.15**	1.36±0.29*	1.80±0.20

x = mean, SD =standard deviation, TP =total proteins, Glu =glucose, Chol =cholesterol, Bil=bilirubine, TG = triglycerides, * = P<0.05, ** = P<0.01

Changes in the enzymatic activity are often linked with the liver damage. ALT and AST are markers of hepatocellular injury (*Abu and Uchendu, 2010*) while ALP is a marker of cholestasis (*Kaneko et al., 1997*). The significant elevation in the activities of AST and ALT in the serum of test animals in group E3 (AST) and all intraperitoneal groups (ALT) suggests that nickel might induce hepatocellular injury in rats. These enzymes are usually raised in acute hepatotoxicity, but tend to decrease with prolonged intoxication, as a result of severe damage to the liver, the increased permeability, damage and necrosis of cells (*Cornelius, 1979, Raquel et al., 1997*). In fact, the increased concentrations of both enzymes were found in acute period of nickel effect and insignificant decrease appeared after the long-term nickel exposure in our experiments. Our results support findings of *Adjroud (2013)*. Author noted an increase in plasma AST after the administration of 25 and 50 mgNiCl₂/kg subcutaneously. Moreover, a significant increase in plasma ALT levels was observed with the administration of 25 mg/kg of NiCl₂ which was the same concentration as used in our experiment, even if it was administered subcutaneously. Ni-induced liver damage was clearly shown in the study of *Pari and Prasath (2008)* by the increased activities of serum hepatic enzymes namely AST, ALT, ALP, gamma glutamyl transferase (GGT) and lactate dehydrogenase (LDH) along with increased elevation of lipid peroxidation indices (thiobarbituric reactive acid substances and lipid hydroperoxides). The toxic effect of Ni was also indicated by significantly decreased levels of enzymatic (superoxide dismutase - SOD, catalase – CAT, glutathione peroxidase - GPx and glutathione S-transferase - GST) and non-enzymatic antioxidants (glutathione - GSH, vitamin C and vitamin E). *Sidhu et al. (2004)* was also able to observe significant elevation in serum AST, ALT and ALP concentrations in rats. However, authors used 8 times higher nickel concentration in drinking water than was realized in our experimental group E4. In another experiment with fish, total protein, AST, ALT and ALP increased and could be used as important and sensitive biomarkers in ecotoxicological studies concerning the effects of metal contamination (*Heydarnejad et al., 2012*). Glutamate dehydrogenase (GLDH) is also accurate marker of hepatocellular injury. The nickel exposure in our experiments was only effective when administered in drinking water. Anyway, the changes even if significant were decreased. This is not important finding from the diagnostic point of view.

Table 3:

Enzymatic profile of the control and experimental rats

Enzyme	Group (x±SD)				
	Control (n=10)	E1 – 15 mg/kg (n=10)	E2 – 25 mg/kg (n=10)	E3 – 35 mg/kg (n=10)	E4 – 100 mg/L (n=10)
AST (μkat/L)	4.83±1.97	6.44±2.74	6.86±2.65	8.66±0.59*	4.17±1.29
ALT (μkat/L)	0.99±0.16	1.46±0.31*	0.68±0.11*	1.77±0.18**	0.89±0.19
ALP (μkat/L)	1.64±1.21	4.39±0.98**	2.74±0.97*	2.71±0.42*	4.15±0.54*
GLDH (μkat/L)	0.46±0.21	0.38±0.10	0.31±0.03	0.37±0.04	0.26±0.09*

x = mean, SD = standard deviation, AST = aspartate aminotransferase, ALT = alanine aminotransferase, ALP = alkaline phosphatase, GLDH = glutamate dehydrogenase, * = P<0.05, ** = P<0.01

Conclusions

The results of the present study suggest that nickel is a potent metal which can cause significant changes in blood biochemistry when administered intraperitoneally or perorally. Changes in mineral profile as well as energy, nitrogen and enzymatic profiles suggest the kidney and liver damage. The most affected parameters of blood were calcium, potassium, glucose, bilirubine, triglycerides, ALT and ALP.

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