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NANOCHROMIUM AND KIDNEY FUNCTION IN THE EXPERIMENT

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Abstract

Excretory kidney function under conditions of water diuresis was examined in the experiments performed on mature laboratory rats exposed to nanochromium citrate administration during 14 days in increasing doses. The degree of nanochromium citrate effect produced on kidney function was found to depend on the dose of the compound injected. Under nanochromium citrate effect in the dose of 0,01 mg/kg ($^1/_{400}$ from DL_{50}) with underlying water loading diuresis increases, the concentration and excretion of sodium ions grows, glomerular filtration rate becomes higher with retention of potassium ions in the body. An increased dose to 0,04 mg/kg ($^1/_{100}$ from DL_{50}) causes occurrence of nephrotoxicity with underlying hyperkalemia, glomerular filtration rate decreases, hyperazotemia and renal loss of protein increase.

Keywords: *chromium as a trace element, nanochromium citrate, kidney function, «dose-effect»*

Introduction

Chromium (Cr^{3+}) as a chemical element has been known since the beginning of the XIX century. It is widely spread in nature (<0,1 mkg/m^3 in the air, 0,03% in the Earth crust, 0,05-0,5 mkg/L in sea water). It is contained in plant and animal products [1, 2]. Chromium compounds are used in electric and electronic equipment, in metallurgy to get heat-resistant and stainless steel, production of heaters, furnace equipment, in manufacturing ferrochromium, pigments etc. In the process of extraction of chromium deposits, burning wood, paper, fuel etc. Cr^{3+} is oxidized into more toxic Cr^{6+}, threatening human health and life [3]. Cr^{3+} as a trace element if essential for normal vital activity of man and animals, since it plays an important role in metabolism, functioning of organs and systems [2, 4].

In recent years the world interest in receiving and use of nanomaterials has been increasing [5, 6]. Due to the fact that in a nanometer range chemical substances can acquire different properties, many scientists direct their attention to the study of biological activity and safety to use nanocompounds. Chromium nanoparticles can be promising in medical practice as well [7].

Ukrainian Scientific-Research Institute of Nanobiotechnologies and Resource-Saving ("Nanomaterials and Nanotechnology", Kyiv) received organic chromium compound – nanochromium citrate (NCC) [8] by means of electric pulse aquananotechnology, which is recommended to use as a food additive in the veterinary practice due to its positive effect on metabolic processes in the body [9, 10]. In respect of learning toxicological characteristics of NCC to investigate its effect on the function of organs participating in metabolic processes, elimination, excretion, including kidneys in particular, seems to be reasonable [11]. Till now studies in this area have not been performed. The objective of our study is to investigate the effect of organic chromium salt – NCC on the parameters of the kidney excretory function.

Methods

The study was conducted on mature albino rats with body weight 150-180 g, kept on standard dietary intake with free access to water and food under conditions of natural light. NCC effect (200 mg/L) produced on the excretory function of the kidneys was examined during 14 days after each administration of the substance into the peritoneum in the doses of $^1/_{400}$, $^1/_{200}$, $^1/_{100}$ from DL_{50}, corresponding to 0,01 mg/kg, 0,02 mg/kg, 0,04 mg/kg [11]. Water for injections was injected to the control animals in an equivalent volume. 30 minutes after the last injection water load was simulated for both control and experimental animals, which promoted not only forcing diuresis, but enabled to make integrative assessment of the vascular-glomerular apparatus function, proximal and distal nephron segments [12]. To create conditions of water diuresis warm distilled water (37°C) in the volume of 5% from the body weight was introduced into the stomach of animals by means of a metallic probe. Then the animals were placed into individual cages, and urine was collected during the following two hours. The animals were taken out of the experiment by means of a single-stage decapitation under ether anesthesia. The concentration of sodium and potassium ions in the urine and blood plasma was determined by means of flame photometry on FPL-1, creatinine concentration – by means of the reaction with picric acid on the spectrophotometer SP-46, protein concentration in the urine – by means of photocolorimetric reaction with sulfosalicylic acid [13], titrate acids and ammonia – by means of titrimetric method, pH of the urine – on the microbioanalyzer OP - 210 «Redelkys».

In addition to absolute values analysis of the kidney functional state (excretory, ion regulating, acid regulating functions) considered their standardized parameters as well concerning the body weight of animals (per 100 g), and glomerular filtration rate (per 100 mcl of filtrate), estimated according to the clearance of endogenous creatinine [13]. All the studies were carried out in accordance with the criteria outlined in the European Union Directive 2010/63/EU "On the protection of animals used for scientific purposes".

The obtained data were statistically porcessed using the SPSS Statistics 17.0 software. All the data

are represented as a mean ± standard error of the mean (M±m). Estimation of differences between the samples was conducted using a parametric Student's t-test and a nonparametric Mann-Whitney U test. The minimum significance level was $p<0.05$.

Statistical processing of the obtained data was performed using the SPSS Statistics 17.0 software. All data are represented as a mean ± standard error of the mean (M±m). Estimation of the differences between the samples was conducted using a parametric Student's t-test and a nonparametric Mann-Whitney U test. The minimum significance level was $p<0.05$.

Results

In the course of studies repeated administration of increasing doses of NCC during 14 days were found to produce different effect on the parameters of the kidney functional state (see Table 1). Everyday introduction of NCC in the dose of 0,01 mg/kg ($^1/_{400}$ from DL_{50}) promoted increased diuresis, concentration and excretion of sodium ions, decreased concentration and excretion of potassium ions in urine. It resulted in increased Na^+/K^+ coefficient in the urine. Glomerular filtration rate (GFR) increased, the concentration of creatinine in the urine and blood plasma did not differ from the parameters of the control animals. Protein concentration in the urine and its excretion increased inconsiderably. The concentration of potassium ions increased and the concentration of sodium ions decreased inconsiderably in the blood plasma. The parameters of filtration, reabsorption, excretory fraction of sodium ions did not change. Its proximal reabsorption and transport remained on the level of the distal portion of the nephron. Meanwhile, standardized proximal transport of sodium ions decreased concerning GFR (100 mcl). Excretion of hydrogen ions increased inconsiderably, ammonia coefficient increased as well, which promoted urine alkalization (see Table 1).

With administration of NCC in the dose twice as much (0,02 mg/kg) the increase of diuresis was not so marked in comparison with the dose of 0,01 mg/kg (see Table 1). The concentration of potassium ions in the urine and its excretion decreased more considerably. Proximal sodium transport and proteinuria remained on the same level. The concentration of potassium ions in the blood plasma increased in comparison with the control animals. Ammonia coefficient of the urine remained on the previous level. The rest parameters of the kidney functions did not differ from those of the control.

With a higher dose (0,04 mg/kg) diuresis decreased to the level of the control animals. Natriuresis, kaliuresis, Na^+/K^+ coefficient of the urine did not differ from those of the control. At the same time, proteinuria and renal loss of protein increased. GFR decreased resulting in an increased concentration of creatinine in the blood plasma. Hyperkalemia remained stably high. Standardized parameters of proton excretion, and titrate acids and ammonia increased, but it did not considerably influence on pH of the urine.

Discussion

Therefore, while analyzing the results obtained it should be noted that the degree of NCC effect on the excretory, ion regulating, acid regulating kidney functions within the range of the doses examined depends on the dose of the substance administered during the course. Small doses ($^1/_{400}$, $^1/_{200}$ from DL_{50}) promoted less marked changes in the work of kidneys after water load. GFR, the content of creatinine in the urine and blood plasma, renal transport of sodium ions remained on the level of the control parameters, though diuresis increased inconsiderably. Attention should be paid to the decrease of the concentration of potassium ions in the urine and its increase in the blood plasma with underlying inconsiderable decrease of sodium ions concentration. With an increasing dose ($^1/_{100}$ from DL_{50}) diuresis did not differ from the control animals with a stable decrease of kaliuresis and hyperkalemia available. Such retention of potassium in the body can be caused by a reduced activity of aldosterone, defective secretion of potassium ions with a disturbed epithelial function in the distal portion of the nephron, reduced number of functioning nephrons, or penetration of potassium into the blood resulting from tissue damage [14]. Moreover, hyperkalemia can result from extra-renal effects – redistribution of potassium ions from the intracellular space into the extracellular one, which occurs in case of metabolic acidosis, fluctuations of

glucose concentration and insulin in the blood. Additional studies, and first of all, examination of the kidney morphological structure, can help in prioritizing of the factors in this situation.

Protein concentration in the urine of animals increases considerably under NCC effect, which is one of the indicators of nephrotoxicity [14]. The loss of a considerable amount of protein might be associated with functional disorders of the filtration barrier of the glomerular kidney apparatus, or with a reduced ability of the proximal tubules to reabsorb protein. Nephrotoxicity of large doses of NCC is evidenced by a considerable decrease of GFR and retention hyperazotemia. In general, the data obtained offer the basis to suggest that increased doses of NCC promote not only functional disorders of the tubular apparatus of the kidneys, but nephron glomeruli as well, which in case of its long administration can cause renal failure.

The degree of NCC effect on the kidney function depends on the dose of the substance administered. Everyday introduction of NCC in small doses of 0,01 mg/kg causes less pronounced changes in the work of kidneys – diuresis, natriuresis, GFR increase, kaliuresis decreases. High doses to 0,04 mg/kg increase nephrotoxicity – GFR decreases with underlying hyperkalemia, hyperazotemia and kidney loss of protein increase.

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Table 1. Effect of nanochromium citrate administered during 14 days on the kidney function, n= 6

Index	Control	Nanochromium citrate		
		0.01 mg/kg	*0.02 mg/kg*	*0.04 mg/kg*
Diuresis, ml/2 hour/100 g	3.7±0.06	4.5±0.18**	4.2±0.13**	3.8±0.19
Concentration of Na^+ in urine, mmol/L	0.52±0.059	0.63±0.058*	0.58±0.063	0.63±0.079
Excretion of Na^+ with urine, mcmol/2 hour•100 g	1.92±0.653	2.85±0.291*	2.38±0.246	2.54±0.899
Proxim.transport of Na^+, mcmol/100 mcL GF	9.486±0.187	8.189±0.598*	8.220±0.462*	9.33±0.506
Distal transport of Na^+, mcmol /100 mcL GF	0.88±0.156	0.80±0.113	0.77±0.10	1.326±0.074*
Concentration of K^+ in urine, mmol/L	12.17±0.917	6.75±1.083**	4.25±0.292***	13.25±4.292
Excretion of K^+ with urine, mcmol/2 hour•100 g	44.87±3.779	29.77±4.571*	17.73±1.615***	49.79±4.96
Glomerular filtrate (GF), mcL/min•100 g	408.72±53.12	488.83±48.62*	423.99±49.11	264.017±33.78*
Protein concentration in urine, mg/L	0.01±0.004	0.02±0.003*	0.02±0.003*	0.036±0.004*
Protein excretion with urine, mg/L •100 g	0.04±0.013	0.09±0.01**	0.08±0.011*	0.14±0.022**
Ammonia coefficient, units	6.36±0.483	7.45±0.5*	7.95±0.445*	5.99±0.337
pH of urine, units	7.68±0.028	8.05±0.142*	7.85±0.092	7.68±0.042
Concentration of Na^+ in blood plasma, mmol/L	133.76±1.53	120.52±0.61**	122.69±0.89**	123.52±0.92**
Concentration of K^+ in blood plasma, mmol/L	6.58±0.125	8.75±0.333***	9.29±0.688**	8.17±0.167***
Creatinine concentration in blood plasma, mcmol/L	67.0±8.83	63.3±7.67	64.7±6.67	102.0±6.67**

* – p<0.05, **– p<0.01, *** – p<0.001; GF – glomerular filtrate; n – number of animals.