August 30, 2020

PharmacologyOnLine

Archives • 2020 • vol.2 • 156-162

POTENTIALITIES OF HYPOGLYCEMIC ACTIVITY OF CHROMIUM NANOPARTICLES

Sadohurska Kateryna*, Kosuba Rayisa, Gordienko Viktor

Higher State Educational Establishment of Ukraine "Bukovinian State Medical University" Chernivtsi, Ukraine

*sadogurska.katya@ukr.net

Abstract

The issues of diabetes mellitus (DM), as a widely spread disease with severe course and complications, are one of the most urgent in the world. Till 2040 the number of DM patients is estimated to increase to 640 million including 90% of them with type 2 DM. Due to nanotechnologies contemporary science is supplied with new achievements in the fields of nanobiology, nanomedicine, nanopharmacology. Nanoparticles and nano-structured materials have been already used as new remedies, biosensors and appliances for visualization and diagnostics. Considering biological value of chromium as a trace element, chromium nanoparticles can be rather promising structures to be applied in nanomedicine. Under conditions of a long administration of nanochromium citrate (NCC) hypoglycemic effect in normoglycemic animals remains and increases in case the period of compound introduction becomes longer. Results of investigation of NCC anti-hyperglycemic activity against the ground of experimental DM (EDM) found that in addition to substantial decrease of glucose concentration in the blood NCC effect promotes normalization of insulin content in the blood serum of animals and insulin resistance index (HOMA-IR), which is indicative of reduced tolerance of insulin-dependent organs to glucose.

Keywords: *nanochromium citrate, hypoglycemic activity, anti-hyperglycemic efficacy, experimental diabetes mellitus*

Introduction

The issues of diabetes mellitus (DM), as a widely spread disease with severe course and complications, are one of the most urgent in the world [1, 2]. Till 2040 the number of DM patients is estimated to increase to 640 million including 90% of them with type 2 DM [3]. In Ukraine sickness rate of the disease 5-7% increases annually, and now it is more than 2 million of people [4]. In spite of new methods of diagnostics and treatment introduced into medical practice DM remains an important medical and social issue in the world [5].

Significant causes of DM occurrence are urbanization, percentage increase of people with obesity, stresses, aging of the population, sedentary life style, and irrational diets [6, 7]. In addition to genetic factor development of DM can result from uncontrolled intake of glucocorticoids, oral contraceptives, certain diuretics etc [8].

Today type 2 DM is widely spread. Insulin resistance (85%) and dysfunction of pancreatic β-cells play the major role in pathogenesis of the disease. Compensatory hyperinsulinemia and hyperglycemia occur in this case resulting in increased glucose supply into the cells, reduced sensitivity and blockade of insulin receptors. Glucose and fat accumulate in the adipose depot at the expense of hyperinsulinemia resulting in the development of obesity [9].

Lack of essential trace elements directly participating in the regulation of carbohydrate metabolism plays an important part in DM pathogenesis. These elements are chromium, zinc, manganese, vanadium etc [10, 11]. Chromium as an essential trace element is known to enter the body from outside. It participates in the regulation of insulin production and metabolism, provides functioning of the pancreas being a constituent of low molecular organic complex – glucose tolerance factor (GTF), and intensifies insulin action [12].

A close relation is found between chromium deficiency in the human organism and occurrence of DM [13]. 33-37% decrease of chromium level (in the blood, hair, tissues) is found in case of DM in comparison with healthy individuals. Chromium deficiency increases insulin resistance as one of the main mechanisms in the development of type 2 DM, and additional intake of this element decreases glucose level in the blood HbA1c and insulin resistance [10, 14].

The outline of the XXI century determines developmental rate of nanotechnologies and their introduction into the practical human activity [15]. In recent decades a considerable amount of nanomaterials have been created on the basis of a number of fundamental and applied researches. They are used in more than 400 products associated with electronics, drugs, cosmetics, packing materials for food, automobile parts, clothes etc. Due to nanotechnologies present-day science is supplied with new achievements in the fields of nanobiology, nanomedicine, nanopharmacology [16, 17, 18, 19]. Nanoparticles and nano-structured materials have been already used as new remedies, biosensors and appliances for visualization and diagnostics [20, 21, 22]. Considering biological value of chromium as a trace element, chromium nanoparticles can be rather promising structures to be applied in nanomedicine. Though, scientific literature contains only fragments concerning their biological activity [23, 24]. The interest in making preparations on the basis of nanometals is continuously increasing, which is associated with pharmacological properties of biometals on nanolevel.

Ukrainian Scientific-Research Institute of Nanobiotechnologies and Resource-Saving (Kyiv) received chromium nanocompound – nanochromium citrate (NCC) [25].

Considering a biological value of chromium as a trace element, the present-day science is interested in investigation of effect of the new chromium nanocompound on carbohydrate metabolism and glucose level in the blood in particular.

Methods

NCC effect produced on glucose level in the blood taken from the caudal vein was examined in normoglycemic (intact control) animals in the dynamics against the ground of a long (14 days) intragastric introduction of NCC in the dose of 0,01 mg/kg by means of the glucometer (Accu-Chek Active New, Germany). Antihyperglycemic activity of NCC was examined on the experimental model of DM simulated on 18-month male rats with the body weight of 220–270 g injecting dexamethasone

solution (KRKA, Slovenia) in the dose of 0,125 mg/kg subcutaneously during 14 days [26]. Reference medicine metformin Sandoz (Poland) was used for comparison in the form of water suspension introduced into the stomach of animals by means of a tube in the dose of 200 mg/kg [27, 28]. In addition to dexamethasone experimental animals were given NCC into the stomach in the dose of 0,01 mg/kg or metformin. The animals were divided into four groups: I group – intact rats, II – control pathology, III – dexamethasone + NCC, IV group – dexamethasone + metformin. 10-12 hours before detection of glucose and insulin level in the blood animals were deprived of food with free access to water. Antihyperglycemic properties of NCC were evaluated by glucose concentration in the blood (in dynamics on the 1st, 7th, 14th days) and insulin content in the blood serum (on the 14th day) in comparison with the reference medicine metformin. To evaluate insulin resistance (IR) a mathematic model of insulin-glucose relations Homeostasis Model Assessment (HOMA) was used. Insulin content in the blood serum was determined by means of immune luminescent analysis on the automatic immune chemiluminescent analyzer (Snibe Co., Ltd, PRC) applying the test-set "Maglumi", PRC. Insulin resistance index (HOMA-IR) was calculated by the formula: HOMA-IR=(glucose (mmol/L) • insulin (mcUN/ml)) / 22,5 (constanta) [29]. All 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".

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

Investigation of NCC effect on glucose level in the blood of normoglycemic animals in case of a long introduction of the compound in to the stomach was indicative of the fact that a day after administration glucose level in the blood did not differ from that of the control indices. 7 days after NCC administration glucose concentration in the blood 13% decreased, 14 days after – 44% decreased in comparison with the intact control (see Table 1).

The study of antihyperglycemic activity of NCC in the process of simulating experimental DM determined that a day after dexamethasone injection and simultaneous NCC or metformin administration glucose concentration in the blood of animals ranges within the levels of intact rats. 7 days after dexamethasone injection (II group) glucose concentration in the blood of animals increased reliably. 14 days after glycemic increased practically twice as much. Moreover, animals developed polydipsia and polyuria which is a reliable sign of EDM simulation.

Under conditions of simultaneous administration of dexamethasone with NCC or metformin (III-IV group) glucose concentration in the blood of animals on the 7th day increased similarly in comparison with the intact control. On the 14th day, though glucose level in the animals remained on the initial level (similar to that of the 7th day), it appeared to be considerably lower than that in the animals with simulated pathology (see Table 1).

In animals with EDM insulin content in the blood serum on the 14th day increased substantially in comparison with the intact animals. Insulinemia level decreased compared to the control pathology either under NCC effect or metformin administration. In case of EDM insulin-glucose relations (HOMA-IR) appeared to be higher than that of the intact animals. On the contrary, when NCC or metformin was used HOMA-IR decreased and did not differ considerably from the indices of the intact animals (see Table 2).

Discussion

Considering the fact that chromium as a trace element participates in maintenance of normal glucose level in the blood [30] we have examined hypoglycemic activity of NCC in normoglycemic animals and antihyperglycemic effect in animals with EDM.

Under conditions of a long NCC administration hypoglycemic effect was found to remain in normoglycemic animals and increase with a longer

period of compound introduction. On the one hand, the obtained results concerning maintenance of NCC hypoglycemic activity during its long introduction are indicative of the lack of tolerance to repeated NCC administration, and on the other hand – intensification of hypoglycemic activity of the compound. At the same time, the mechanism of its action requires additional studies.

In animals with simulated pathology efficacy of antihyperglycemic action of NCC was compared with the reference drug metformin. Administration of NCC into the stomach was stipulated by several reasons. First, DM caused by dexamethasone injection simulates type 2 EDM in animals, and usually in its treatment oral hypoglycemic drugs are used. Second, specific anti-diabetic activity of NCC with EDM was compared with the effect of the hypoglycemic drug metformin which is administered in DM patients orally.

A reliable sign of type 2 EDM simulation was glycemia increase on the 14th day after dexamethasone injection [27]. Scientific literature contains information that in case of dexamethasone-induced DM secretory function of pancreatic β-cells is disturbed, insulin resistance develops, tolerance to carbohydrates increases [26]. NCC administration in animals with EDM decreased glucose level in the blood which did not differ considerably from metformin antihyperglycemic effect. Insulinemia decreased under effect of NCC or metformin against the ground of EDM. Due to low sensitivity of the peripheral tissues to insulin effect with EDM HOMA-IR was higher than that of the intact animals. And on the contrary, after administration of NCC or metformin HOMA-IR decreased respectively and did not differ much from the indices of the intact animals. The results obtained evidenced that antihyperglycemic effect of NCC with EDM is similar to that of the reference medicine metformin. According to literature data sugar-reducing activity of metformin as a reference anti-diabetic agent is known to be caused by its action on various stages of carbohydrate metabolism in the body: reduced tissue resistance to insulin; increased glucose utilization by the muscular and adipose tissues; inhibition of glucose biosynthesis in the liver; decreased absorption of glucose from the intestines [28]. Additional studies on a comprehensive mechanism of anti-diabetic activity of NCC can help to understand which of the above mechanisms is preferred in case of NCC action including its action on the pancreatic β-cells.

Conclusion. The results of experimental studies is indicative of the fact that hypoglycemic activity of NCC in normoglycemic animals remains and intensifies as the evidence of lack of tolerance with repeated administration. Glucose concentration in the blood, insulin content in the blood serum and insulin resistance of the tissues (HOMA-IR) decrease against the ground of simulated pathology (EDM) in comparison with the control pathology and reaches the level of the intact animals. The results obtained substantiate reasonability to conduct further studies on investigation of pathogenic mechanisms of hypoglycemic action and antihyperglycemic activity of NCC as a promising anti-diabetic agent.

References

1. Crawford, K. (2017). Review of 2017 diabetes standards of care. Nurs Clin North Am, 52(4), 621-663.
2. Telishevka, M., Chenett, L., McKee, M. (2001). Towards an understanding of the high death rate among young people with diabetes in Ukraine. Diabet Med, 18(1), 3-9.
3. Ogurtsova, K., Fernandes, J., Huang, Y., Linnenkamp, U., Guariguata, L., Cho N.H., & Makaroff, L. (2017). IDF Diabetes Atlas: Global Estimates for the Prevalence of Diabetes for 2015 and 2040. Diabetes Res Clin Pract, 128, 40-50.
4. Khalangot, M.D., Kovtun, V.A., Gurianov, V.G., Pysarenko, Y.M., Kravchenko, V.I. (2019). Evaluation of type 2 diabetes prevention through diet modification in people with Impaired glucose regulation: a population-based study. Prim Care Diabetes, 13(6), 535-541.
5. Zimmet, P.Z., Magliano, D.J., Herman, W.H., Shaw, J.E. (2014). Diabetes: A 21st Century Challenge. Lancet Diabetes Endocrinol, 2(1), 56-64.
6. Maksymets, T., Karpyshyn, N., Gutor, T., Sklyarova, H., Sklyarov, E. (2018). Influence of risk factors on insulin resistance in

patients with overweight and obesity. Wiad Lek, 71, 558-560.
7. Hackett, R.A., Steptoe, A. (2017). Type 2 Diabetes Mellitus and Psychological Stress - A Modifiable Risk Factor. Nat Rev Endocrinol, 13(9), 547-560.
8. Kozak, B.M., Tjota, M.Y., Close, K.L. (2012). International Diabetes Federation (IDF) highlights growing global impact of diabetes in 5th edition of the Diabetes Atlas. Journal of Diabetes, 4, 8-17.
9. Mandrik, O., Severens, J.L., Doroshenko, O., Pankiv, V., Kravchun, N., Vlasenko, M. (2013). Impact of Hypoglycemia on Daily Life of Type 2 Diabetes Patients in Ukraine. J Multidiscip Healthc, 6, 249-257.
10. Cefalu, W.T., Hu, F.B. (2004). Role of chromium in human health and in diabetes. Diabetes Care, 27(11), 2741-2751.
11. Kazi, T.G., Afridi, H.I., Kazi, N., Jamali, M.K., Arain, M.B., Jalbani, N., & Ghulam, A.K. (2008). Copper, Chromium, Manganese, Iron, Nickel, and Zinc Levels in Biological Samples of Diabetes Mellitus Patients. Biol Trace Elem Res, 122(1), 1-18.
12. Jeejeebhoy, K.N. (1999). Chromium and parenteral nutrition. Trace Elements in Experimental Medicine, 12(2), 85-89.
13. Lewicki, S., Zdanowski, R., Krzyżowska, M., Lewicka, A., Dębski, B., Niemcewicz, M., & Goniewicz, M. (2014). The role of Chromium III in the organism and its possible use in diabetes and obesity treatment. Ann Agric Environ Med, 21(2), 331-335.
14. Paiva, A.N., Lima, J.G., Medeiros, A.C., Figueiredo, H.A., Andrade, R.L., Ururahy, M.A., & Maria, G. (2015). Beneficial Effects of Oral Chromium Picolinate Supplementation on Glycemic Control in Patients With Type 2 Diabetes: A Randomized Clinical Study. J Trace Elem Med Biol, 32, 66-72.
15. He, X., Deng, H., Hwang, H.M. (2019). The Current Application of Nanotechnology in Food and Agriculture. J Food Drug Anal, 27(1), 1-21.
16. Yigit, M.V., Moore, A., Medarova, Z. (2012). Magnetic nanoparticles for cancer diagnosis and therapy. Pharm Res, 29(5), 1180-1188.
17. Yohan, D., Chithrani, D. (2014). Applications of nanoparticles in nanomedicine. J Biomed Nanotechnol, 10(9), 2371-2392.
18. Ventola, C.L. (2017). Progress in Nanomedicine: Approved and Investigational Nanodrugs. P&T, 42(12), 742-755.
19. Teli, M.K., Mutalik, S., Rajanikant, G.K. (2010). Nanotechnology and nanomedicine: going small means aiming big. Curr Pham Des, 16, 1882-1892.
20. Chekman, I.S. (2013). Wave Properties of Nanoparticles: The View of a Problem. Lik Sprava, (7), 3-8.
21. Choi, J.W., Oh, B.K., Kim, Y.K., Min, J. (2007). Nanotechnology in Biodevices. J Microbiol Biotechnol, 17(1), 5-14.
22. Malekzad, H., Zangabad, P.S., Mirshekari, H., Karimi, M., Hamblin, M.R. (2017). Noble metal nanoparticles in biosensors: recent studies and applications. Nanotechnol Rev, 6(3), 301-329.
23. Zha, L., Xu, Z., Wang, M., Gu, L. (2007). Effects of chromium nanoparticle dosage on growth, body composition, serum hormones and tissue chromium in Sprague-Dawley rats. J Zhejiang Univ Sci B, 8(5), 323-330.
24. Chandra, S., Kumar, A. (2013). Spectral, thermal and morphological studies of chromium nanoparticles. Spectrochim Acta A Mol Biomol Spectrosc, 102, 250-255.
25. Kosinov, M.V., Kaplunenko, V.H. (2008). Sposib otrymannya akvakhelativ nanometaliv «Eroziyno-vybukhova nanotekhnolohiya otrymannya akvakhelativ nanometaliv» [Method of obtaining nanometals aqua chelates "Erosion-explosive nanotechnology of obtaining nanometals aqua chelates"] (Ukraine Patent identifier № 29856), 2008.
26. Stefanov, O.V. (2001). Doklinichni doslidzhennya likars'kykh zasobiv [Preclinical studies of medicines]. Kyiv: Avitsena.
27. Poltorak, V.V. (2000). Vplyv metforminu na rozvytok insulinorezystentnosti, indukovanoyi deksametazonom u shchuriv. [Effect of metformin on the development of dexamethasone-induced insulin resistance in

rats]. Endokrynolohiya [Endocrinology], 5, (2), 249-251.
28. Zhou, T., Xu, X., Mengfan, D., Zhao, T., Wang, J. (2018). Preclinical overview of metformin for the treatment of type 2 diabetes. Biomed Pharmacother, 106, 1227-1235.
29. Matthews, D.R., Hosker, J.P., Rudenski, A.S. (1985). Homeostasis model assessment: insulin resistance and betta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia, 28(7), 412-419.
30. Pechova, A., Pavlata, L. (2007). Chromium as an essential nutrient: a review. Veterinarni Medicina, 52,(1), 1-18.

Table 1. Glycemia dynamics in normoglycemic rats in the process of simulating diabetes mellitus

Conditions of the experiment	Glucose content in the blood, mmol/L		
	1 day	7 day	14 day
Intact control	*5.30±0.20*	*5.40±0.07*	*5.47±0.21*
Nanochromium citrate	*5.12±0.2*	*4.72±0.2*$^{\#}$	*3.05±0.3*$^{\#}$
Control pathology	*5.37±0.26*	*7.20±0.20*$^{\#}$	*14.22±0.36*$^{\#}$
Dexamethasone + nanochromium citrate	*5.52±0.19*	*6.47±0.30*$^{\#}$	*6.63±0.34*$^{\#*}$
Dexamethasone +metformin	*5.65±0.16*	*7.05±0.35*$^{\#}$	*6.98±0.41*$^{\#*}$

$^{\#}$p<0.05 reliable difference compared to that of intact control; *p<0.05 reliable difference compared to that of control pathology

Table 2. Nanochromium citrate effect on glucose level, insulin content in the blood of rats and insulin resistance (HOMA-IR) against the ground of experimental DM on the 14th day

Conditions of the experiment	Control (intact animals)	EDM (control pathology)	EDM+NCC	EDM+ metformin
Glucose content in the blood, mmol/L	*5.47±0.21*	*14.22±0.36*$^{\#}$	*6.63±0.34*$^{\#*}$	*6.98±0.41*$^{\#*}$
Insulin, mcUN/ml	*1.9±0.15*	*4.2±0.20*$^{\#}$	*1.8±0.09**	*1.6±0.06**
HOMA-IR, st.un.	*0.46±0.03*	*3.33±0.26*$^{\#}$	*0.52±0.03**	*0.49±0.04**

$^{\#}$p<0.05 reliable difference compared to that of intact control; *p<0.05 reliable difference compared to that of control pathology