

ИССЛЕДОВАНИЕ ВЛИЯНИЯ КОМПЛЕКСОВ ИОНОВ 3d-МЕТАЛЛОВ С ГЛЮКОНОВОЙ КИСЛОТОЙ НА СИНТЕЗ ЦИТОКИНОВ ПРИ ЭКСПЕРИМЕНТАЛЬНОМ ИММУНОДЕФИЦИТЕ

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Цель. Оценка влияния синтезированных глюконатов 3d-металлов на продукцию цитокинов в сыворотке крови мышей с экспериментальным иммунодефицитом (ИД). **Материалы и методы.** Исследовали влияние комплексных соединений двухвалентных 3d-металлов (Mn, Fe, Co, Cu, Zn) с глюконовой кислотой на продукцию цитокинов: интерлейкина (ИЛ)-1 β , ИЛ-6, интерферона- γ (ИФН- γ), фактора некроза опухоли α (ФНО- α) в сыворотке крови мышей с ИД, индуцированным путем однократного внутрибрюшинного введения циклофосамида в дозе 50 мг/кг. Пероральное введение глюконатов 3d-металлов (10^{-2} моль/л) в сравнении с иммуностимулирующим препаратом «Ликопид®» и глюконатом кальция (дозы рассчитывали согласно инструкции) проводили ежедневно в течение 2-х недель, начиная со 2-х суток после инъекции циклофосамида. Уровень цитокинов определяли методом иммуно-ферментного анализа. **Результаты.** На 16-е сутки после индуцирования ИД в сыворотке крови мышей происходило снижение уровня цитокинов: ИЛ-1 β – на 75%, ИЛ-6 – на 65,2%, ИФН- γ – на 61,6%, ФНО- α – на 55,6% (для всех $p < 0,05$). Глюконаты 3d-металлов оказывали стимулирующее действие на синтез цитокинов в зависимости от используемого металла: MnGl, FeGl, CoGl, CuGl – менее эффективное, чем ликопид. ZnGl оказывал более слабое влияние по сравнению с ликопидом только на синтез ИЛ-6, на секрецию ИЛ-1 β и ИФН- γ – подобное ликопиду, а ФНО- α – в большей степени (для всех сравнений $p < 0,05$). Глюконат кальция не оказывал значимого влияния на содержание цитокинов. **Заключение.** Полученные результаты свидетельствуют о значимой роли 3d-металлов в поддержании иммунного гомеостаза, что с учетом данных литературы можно объяснить их действием через активацию нуклеарного фактора транскрипции NF- κ B, контролирующего экспрессию цитокинов.

Ключевые слова: комплексы, 3d-металлы, глюконовая кислота, цитокины, мыши, иммунодефицит.

A STUDY OF THE EFFECT OF COMPLEXES OF 3D-METAL IONS WITH GLUCONIC ACID ON SYNTHESIS OF CYTOKINES IN EXPERIMENTAL IMMUNODEFICIENCY

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Aim. Evaluation of the influence of synthesized gluconates of 3d-metals on production of cytokines in blood serum of mice with experimental immunodeficiency. **Materials and Methods.** The effect of complex compounds of bivalent 3d-metals (Mn, Fe, Co, Cu, Zn) with glucuronic acid on production of cytokines: interleukin (IL)-1 β , IL-6, interferon- γ (IFN- γ), tumor necrosis factor- α



(TNF- α) in blood serum of mice with experimental immunodeficiency induced by a single intraperitoneal administration of cyclophosphamide at the dose of 50 mg/kg was studied. 3d-Metal gluconates (10^{-2} mol/l) were orally introduced for comparison with immunostimulatory drug «Licopid®» and calcium gluconate (doses were calculated according to the instructions) daily for two weeks, starting from the second day after the injection of cyclophosphamide. Levels of cytokines were determined by immunoenzyme analysis. **Results.** On the 16th day after the induction of immunodeficiency, levels of cytokines in blood serum of mice decreased: IL-1 β – by 75.0%, IL-6 – by 65.2%, IFN- γ – by 61.6%, TNF- α – by 55.6% ($p < 0.05$). Stimulatory effect of gluconates of 3d-metals on synthesis of cytokines depended on the used metal: the effect of MnGl, FeGl, CoGl, CuGl was lower than of licopid. ZnGl produced a weaker effect than licopid only on synthesis of IL-6, and equal effect on secretion of IL-1 β and IFN- γ , and the highest effect on TNF- α ($p < 0.05$ for all comparisons). Calcium gluconate did not produce any significant effect on the content of cytokines. **Conclusion.** The obtained results show a significant role of 3d-metals in maintenance of immune homeostasis, which, taking into account the literature data, may be explained by their action through activation of the nuclear transcription factor NF- κ B which controls expression of cytokines.

Keywords: complexes, 3d-metals, gluconic acid, cytokines, mice, immunodeficiency.

Synthesis and study of the effect of complexes of 3d-metal ions with gluconic acid, their participation in the vital processes, and their probable application in medicine, is one of priority directions of modern biochemistry.

Cytokines are a group of hormone-like proteins and peptides with a low molecular weight (<30 kDa) that model interactions of cells in different immune and inflammatory processes in an organism, and link congenital immunity with adaptive immunity [1]. At present there is no doubt that the system of cytokines plays a defining role in development of different diseases involving the immune system.

Aim of study was to evaluate the influence of synthesized 3d-metal gluconates on production of cytokines in blood serum of mice with experimental immunodeficiency (ID).

Materials and Methods

The work was conducted on sexually mature mice – 2.5-3-month males of 25-28 g mass obtained from the mouse bank «Immunopreparat» (Ufa). Gluconates of 3d-metals were synthesized by us in advance in Ufa Institute of Chemistry UFRS RAS [2]. Experimental ID was induced by a single intraperitoneal introduction of cyclophosphamide (Endoxan®, Baxter AG, Switzerland) at the dose of 50 mg/kg.

For comparison, licopid [4-O-(2-acetylamino-2-deoxy- β -D-glucopyranosyl)-N-acetylmuramyl]-L-alanyl-D- α -glutamylamide) (OOO Peptek, Russia) – a synthetic analog to glycopeptides of bacterial wall possessing a high immunomodulatory activity, and also calcium gluconate were used. The choice of the second comparison drug was based on the fact that in the complexes of the studied gluconates of 3d-metals, gluconic acid is present in the form of gluconate-ion, and for comparison a compound should be used containing gluconate-ion without 3d-element.

The mice were divided into 9 groups (n=12 each): the 1st group included intact animals; the 2nd group included animals with ID without treatment, 3^d group – animals with ID and introduction of licopid, 4th group – with ID and introduction of calcium gluconate, 5th-9th groups with ID and 3d-metal gluconates ((5th group – manganese gluconate (MnGl), 6th group – ferrum gluconate (FeGl), 7th group – cobalt gluconate (CoGl), 8th group – copper gluconate (CuGl), 9th group – zinc gluconate (ZnGl)).

Peroral introduction of 3d-metal gluconates and of comparison drugs started on the 2nd day after injection of cyclophosphamide and then daily within 14 days.

All drugs were diluted in distilled water and introduced perorally 0.2 mL daily, in a day after intraperitoneal introduction of cyclophosphamide in the calculated doses: lico-
pid – 0.025 mg/mL according to the instruction (0.14-0.28 mg/kg); calcium gluconate – on the basis of the daily dose for a human (according to the instruction 5-6 g) with re-
calculation for an average weight of a mouse (25 g) – 2.15 mg, or $5 \cdot 10^{-6}$ mol; 3d-metal glu-
conates (3d MeGl) in the concentration of 10^{-2} mol/L, according to the published data and doses accepted in medical practice.

On the 16th day the animals were with-
drawn from the experiment, and blood was tak-
en with separation of serum by centrifugation.

All manipulations with animals were
conducted according to Declaration of Hel-

sinki on humane treatment of animals and to
Order №267 «Of Rules of Good Laboratory
Practice» of June 19, 2003.

The level of cytokines: interleukin-1 β
(IL-1 β), interleukin-6 (IL-6), interferon- γ
(IFN- γ) and tumor necrosis factor- α (TNF- α)
was determined by IFA method using test kits
(FSUIHPBFMBA, St. Petersburg, Russia).

Statistical processing of the obtained re-
sults was conducted using Statistica 10.0 pro-
gram (Stat Soft Inc., USA), with determina-
tion of median (Me) and interquartile range
(Q₁-Q₃). Statistical significance of differences
between the groups was evaluated using non-
parametric Mann-Whitney test. The values were
considered statistically significant at $p < 0.05$.

Results and Discussion

The results of study are given in Table 1.

Table 1

Influence of 3d-Metal Gluconates on Production of Cytokines (IL-1 β , IL-6, IFN- γ , TNF- α) in Blood Serum of Mice with Experimental ID

Groups of Mice	Statistical Parameter	Cytokines			
		IL-1 β , pg/mL	IL-6, pg/mL	IFN- γ , pg/mL	TNF- α , pg/mL
1. Control - Intact animals (n=12)	M \pm σ Me [Q ₁ -Q ₃]	5.6 \pm 0.6 5.64 [5.0-6.2]	47.5 \pm 4.8 48.2 [42.9-52.3]	7.5 \pm 0.8 7.6 [6.7-8.3]	30.9 \pm 3.2 31.3 [27.8-34.1]
2. Control - ID without treatment (n=12)	M \pm σ Me [Q ₁ -Q ₃] <i>p</i> ₁₋₂	1.4 \pm 0.2 1.41 [1.2-1.6] 0.00003	16.6 \pm 1.7 16.8 [15.0-18.3] 0.00003	2.9 \pm 0.4 2.92 [2.5-3.3] 0.0326	13.4 \pm 1.4 13.6 [12.1-14.8] 0.00003
3. ID + lico- pid (n=12)	M \pm σ Me [Q ₁ -Q ₃] <i>p</i> ₂₋₃	4.8 \pm 0.6 4.84 [4.2-5.4] 0.00003	42.5 \pm 4.5 43.1 [38.2-47.0] 0.00003	7.2 \pm 0.8 7.3 [6.4-8.0] 0.00003	24.5 \pm 2.6 24.6 [23.1-27.1] 0.00003
4. ID + CaGl (n=12)	M \pm σ Me [Q ₁ -Q ₃] <i>p</i> ₂₋₄	1.5 \pm 0.16 1.5 [1.3-1.6] 0.1939	17.3 \pm 1.8 17.5 [15.6-19.1] 0.2482	3.2 \pm 0.4 3.22 [2.8-3.6] 0.0734	13.8 \pm 1.5 14.0 [12.3-15.3] 0.3263
5. ID + MnGl (n=12)	M \pm σ Me [Q ₁ -Q ₃] <i>p</i> ₂₋₅ <i>p</i> ₃₋₅ <i>p</i> ₄₋₅	2.7 \pm 0.3 2.73 [2.4-3.0] 0.00003 0.00003 0.00003	26.3 \pm 2.7 26.6 [23.7-29.0] 0.00003 0.00003 0.00003	4.9 \pm 1.6 5.1 [3.3-6.5] 0.0014 0.0008 0.0055	20.9 \pm 2.1 21.2 [18.9-23] 0.00003 0.0018 0.00003
6. ID + FeGl (n=12)	M \pm σ Me [Q ₁ -Q ₃] <i>p</i> ₂₋₆ <i>p</i> ₃₋₆ <i>p</i> ₄₋₆	2.3 \pm 0.3 2.33 [2.0-2.6] 0.00003 0.00003 0.00003	20.4 \pm 2.2 20.7 [18.3-22.6] 0.0004 0.0004 0.0038	3.5 \pm 0.4 3.52 [3.1-3.9] 0.0038 0.00003 0.0734	14.3 \pm 1.5 14.5 [12.8-15.8] 0.119 0.00003 0.3263

7. ID + CoGl (n=12)	M±σ	2.8±0.3	19.6±2.0	4.9±0.5	16.4±1.7
	Me	2.83	19.8	5.0	16.6
	[Q ₁ -Q ₃]	[2.5-3.1]	[17.7-21.6]	[4.4-5.4]	[14.8-18.1]
	p ₂₋₇	0.00003	0.0026	0.00003	0.00003
	p ₃₋₇	0.00003	0.00003	0.00003	0.00003
8. ID + CuGl (n=12)	M±σ	3.9±0.5	29.2±3.0	5.6±0.6	21.8±2.2
	Me	4.0	29.6	5.64	22.1
	[Q ₁ -Q ₃]	[3.4-4.4]	[26.3-32.2]	[5.0-6.2]	[19.7-24.0]
	p ₂₋₈	0.00003	0.00003	0.00003	0.00003
	p ₃₋₈	0.0029	0.00003	0.0001	0.0153
9. ID + ZnGl (n=12)	M±σ	4.7±0.5	38.2±3.9	7.1±0.8	27.4±2.8
	Me	4.8	38.7	7.19	27.8
	[Q ₁ -Q ₃]	[4.2-5.2]	[34.5-42.1]	[6.2-7.9]	[24.7-30.2]
	p ₂₋₉	0.00003	0.00003	0.00003	0.00003
	p ₃₋₉	0.5833	0.0326	0.6236	0.0326
	p ₄₋₉	0.00003	0.00003	0.00003	0.00003

Note: p_{2-n}<0.05 – statistically significant differences with the control group «ID without treatment»; p_{3-n} and p_{4-n}<0.05 – statistically significant differences with comparison groups: «ID + Licopid» and «ID + CaGl»

It is seen from Table 1, that in ID induced by injection of cyclophosphamide, the level of cytokines in blood serum of mice decreased: IL-1β – by 75.0%, IL-6 – by 65.2%, IFN-γ – by 61.6%, TNF-α – by 55.6% (for all p<0.05).

After a course of treatment with Licopid drug, production of cytokines in comparison with control group «ID without treatment» increased: IL-1β – by 61.8%, IL-6 – by 54.6%, IFN-γ – by 57.6%, TNF-α – by 35.2% (for all p<0.05). Here, calcium gluconate did not produce any significant effect on the concentration of the studied cytokines (for all cytokines p>0.05).

Introduction of 3d-metal compounds with gluconic acid induced production of cytokines, both of proinflammatory (IL-1β, IL-6, TNF-α), and of anti-inflammatory (IFN-γ), depending on the metal used: the effect of MnGl, FeGl, CoGl, CuGl was lower (p<0.05) than in the group «ID + licopid». Here, the effect of ZnGl was weaker than of licopid only on synthesis of IL-6; its action on secretion of IL-1β and IFN-γ was comparable to that of licopid, and was strongest on secretion of TNF-α (p<0.05).

In comparison with the control group «ID without treatment», synthesis of cyto-

kines under influence of 3d-metal gluconates increased in the following way:

1) under action of MnGl: IL-1β – by 23.4%, IL-6 – by 20.4%, IFN-γ – by 28.7%, TNF-α – by 24.3%;

2) under action of FeGl: IL-1β – by 16.3%, IL-6 – by 8.1%, IFN-γ – by 7.9%, TNF-α – without change;

3) under action of CoGl: IL-1β – by 25.2%, IL-6 – by 6.3%, IFN-γ – by 27.3%, TNF-α – by 9.6%;

4) under action of CuGl: IL-1β – by 45.9%, IL-6 – by 26.6%, IFN-γ – by 35.8%, TNF-α – by 27.2%;

5) under action of ZnGl: IL-1β – by 60.1%, IL-6 – by 45.5%, IFN-γ – by 56.2%, TNF-α – by 45.4% (p<0.05).

IL-1 is the first representative of the family of structurally related cytokines having two isoforms – α and β. It is shown that IL-1β is a key activator of NFκB – regulated (kappa-B complex of nuclear factor) genes, and triggers transcription under action of different agents [3] including immunostimulatory ones which are compounds with gluconic acid used in the given work [4].

IL-6 is one of the key proinflammatory cytokines playing a significant role in development of many diseases since increase in its

level is noted in many inflammatory processes and malignant diseases [5]. At the same time it can manifest anti-inflammatory properties because it is synthesized by activated macrophages and T-cells and stimulates immune response of an organism.

IFN- γ activates normal killer cells, phagocytes and induces formation of granulomas that play a barrier function against intracellular pathogens.

TNF- α is a proinflammatory cytokine synthesized by hematopoietic and non-hematopoietic cells and is considered to be an agent that links inflammation with development of tumor [6]. TNF- α mostly acts through TNFR₁ receptor and activates NF- κ B transcription factor [7] inducing cell apoptosis through activation of caspases [8]. Proinflammatory action of TNF- α consists in increase in production of different molecules: protein growth factors, metalloproteinase enzymes, eicosinoids of prostaglandins and leukotrienes, and of proinflammatory cytokines [9].

It is known that a significant role in the immune response is played by NF- κ B nuclear transcription factor that consists of a combination of proteins binding with DNA [10]. It was shown that production of proinflammatory cytokines (TNF- α , IL-1, IL-6) depends on expression of synthesis of this nuclear factor which is normally bound with I κ B protein. Proinflammatory cytokines (e.g., TNF- α , IL-1, IL-6) activate complex I κ B kinase which catalyzes reaction of phosphorylating of I κ B protein on its serine residue (in positions 32 and 36) which leads to activation of NF- κ B factor and to breakage of its bond with I κ B α . In turn, NF- κ B activation increases synthesis of TNF- α and IL-6, and, accordingly, promotes increase in production of other cytokines [11].

The results of this work showed that the most evident effect on production of cytokines was produced by zinc gluconate. It is known from the literature that activation of NF- κ B factor is determined by the presence of zinc ions [12]. Comparison of these results about the role of NF- κ B factor controlling expression of cytokines and activated by zinc ions, permits to make a conclusion about immunostimulatory action of zinc gluconate through production of cytokines which, in turn, induces production of antibodies through activation of the nuclear transcription factor.

Significant influence of other 3d-metal gluconates on increase in the level of cytokines in blood serum of immunodeficient mice shows that they also play an important role in the activation of synthesis of cytokines. Here, introduction of calcium gluconate did not reveal any differences with the parameters of the group of immunodeficient mice «without treatment» which emphasizes the defining role of the above compounds of 3d-metals.

Conclusion

3d-Metal gluconates induce production of cytokines (interleukin 1 β , interleukin 6, interferon γ , tumor necrosis factor α) in mice with experimental immunodeficiency, and to a larger extent in the immune homeostasis.

Comparison of the obtained results with the literature data about the role of NF- κ B nuclear transcription factor that controls expression of cytokines and is activated in the presence of zinc ions, indicates a probable mechanism of the immunocorrecting effect of these compounds mediated through activation of transcription factor that induces synthesis of cytokines which in turn stimulate production of antibodies.

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Дополнительная информация [Additional Info]

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