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Content of Bone Morphogenetic Proteins in Blood Plasma of Rats with Metabolic Syndrome during Mandibular Defect Restoration

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ABSTRACT

The aim was to study the concentration of bone morphogenetic proteins-2 (BMP) and -7 in the blood plasma of rats with metabolic syndrome during reparative osteogenesis in mandibular defect.

Materials and methods. The experiments were carried out on male Wistar rats, which were divided into 4 groups: 1) native; 2) control (with mandibular defect); 3) metabolic syndrome; 4) experimental (with metabolic syndrome and mandibular defect). Metabolic syndrome was simulated by replacing standard feed with a high-fat and high-carbohydrate diet. The development of metabolic syndrome was confirmed by changes in body weight, glucose and triacylglycerides concentrations in blood plasma. The mandibular defect was formed in rats according to the method proposed by Grigoryan et al. The content of BMP-2 and BMP-7 in blood plasma was determined by the enzyme-linked immunoassay on days 7, 14, 21, and 28 after the surgery. We calculated the median and the interquartile range *Me* [Q_1; Q_3] and applied the Mann – Whitney *U*-test and the Bonferroni correction. Differences in indicators were considered to be significant at $p < 0.025$.

Results. A significant increase in the content of the studied proteins in the blood plasma was determined in the group metabolic syndrome compared to the naïve group. BMP-2 and BMP-7 concentration in rats of the control group was higher throughout the experiment compared to the naïve group ($p < 0.025$). In the experimental group, a decrease in the concentration of BMP-2 (on days 7, 14, and 28) and BMP-7 (on days 7–28) was found compared to the control group ($p < 0.025$). An increase in the concentration of BMP-2 and BMP-7 was detected in the experimental group compared to the metabolic syndrome group ($p < 0.025$) on day 7 and on days 7–14, respectively.

Conclusion. A significant decrease in BMP-2 and BMP-7 concentration in the blood plasma was found in rats with metabolic syndrome during mandibular reparative osteogenesis compared to animals without metabolic disorders.

Keywords: metabolic syndrome, mandibular defect, reparative osteogenesis, bone morphogenetic proteins

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Содержание костных морфогенетических белков в плазме крови крыс с метаболическим синдромом при восстановлении дефекта нижней челюсти

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РЕЗЮМЕ

Цель – изучение концентрации костных морфогенетических белков (КМБ) 2 и 7 в плазме крови крыс с метаболическим синдромом в процессе репаративного остеогенеза при дефекте нижней челюсти.

Материалы и методы. Работа выполнена на самцах крыс линии Вистар, из которых сформировали четыре группы: 1) интактная; 2) контрольная – дефект нижней челюсти; 3) метаболический синдром; 4) опытная – метаболический синдром и дефект нижней челюсти. Метаболический синдром моделировали заменой стандартного корма высокожировой и высокоуглеводной диетой. О наличии метаболического синдрома судили по изменениям массы тела, концентрации глюкозы и триацилглицеридов в плазме крови. Дефект нижней челюсти формировали по методу А.С. Григорьяна и соавт. На 7-, 14-, 21- и 28-е сут после операции в плазме крови определяли содержание КМБ-2 и -7 методом иммуноферментного анализа. Рассчитывали медиану и интерквартильный размах Me [Q_1; Q_3], использовали U-критерий Манна – Уитни и поправку Бонферрони. Различия показателей считали значимыми при $p < 0{,}025$.

Результаты. В группе «метаболический синдром» установлено увеличение в плазме содержания исследуемых белков по сравнению с интактной группой. Концентрация КМБ-2 и КМБ-7 у крыс контрольной группы был выше на всем протяжении эксперимента по сравнению с интактной группой ($p < 0{,}025$). В опытной группе установлено снижение концентрации КМБ-2 (на 7-, 14- и 28-е сут) и КМБ-7 (на 7–28 сут) по сравнению с контрольной группой ($p < 0{,}025$). Показано увеличение содержания КМБ-2 на 7-е сут, а КМБ-7 на 7–14 сут в опытной группе по сравнению с группой «метаболический синдром» ($p < 0{,}025$).

Заключение. У крыс с метаболическим синдромом установлено значимое снижение концентрации в плазме крови КМБ-2 и КМБ -7 при заживлении дефекта нижней челюсти по сравнению с животными без метаболических нарушений.

Ключевые слова: метаболический синдром, дефект нижней челюсти, репаративный остеогенез, костные морфогенетические белки

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

Bone morphogenetic proteins (BMPs) belong to the transforming growth factor β superfamily, with BMP-1 being the exception [1]. Currently, more than 20 types of BMPs have been identified, which play a key role in the processes of morphogenesis, cell differentiation, apoptosis, and tissue repair [2]. BMPs are synthesized by osteopregenitor cells, osteoblasts, chondrocytes, platelets, and endothelial cells in various tissues [3]. BMPs stimulate different stages of bone tissue development and the restoration of its integrity after damage [3]. BMPs-2, -4, -5, -6, -7, and -9 exhibit high osteogenic activity, interacting with two types of receptors [2]. The main pathways for the implementation of BMP regulatory effects are Smad-dependent, RUNX2, MKK-ERK1/2, and MKK-ERK1/2 [2]. It is generally accepted that BMP-2 and BMP-7 are the most active stimulators of osteogenic differentiation of mesenchymal stem cells in *in vitro* and *in vivo* models [4]. The transcription factors Runx2 and Dlx5 control the enhancement of osteoblast formation from mesenchymal stem cells [3].

Metabolic disorders alter the production of osteogenesis inducers, which stimulate the restoration of bone integrity following damage [5]. Studies have demonstrated increased activity of the osteopontin and osteoprotegerin genes in experimental type 2 diabetes mellitus in rats [6] and resistance to erythropoietin, which activates osteogenesis [7] in patients with metabolic syndrome (MS) on hemodialysis [8]. Decreased production of BMP-6 by bone callus cells has been observed in rats with streptozotocin-induced type 1 diabetes mellitus [9].

Recently, an alteration of the reparative osteogenesis process in the mandibular defects in MS rats has been demonstrated, manifested by a slowdown in the formation of new bone tissue and its remodeling [10]. However, there are no literature data on the MS effect on BMP production. Therefore, an analysis of BMP levels in MS rats during bone integrity restoration is of interest.

The aim was to study BMP-2 and BMP-7 concentration in the blood plasma of MS rats during reparative osteogenesis in the mandibular defects.

MATERIALS AND METHODS

The experiments were performed on 81 male Wistar rats weighing 200–230 g from the Stolbovaya branch of the Scientific Center for Biomedical Technologies of the Federal Medical and Biological Agency. The experiments were conducted in the preclinical drug research laboratory of the Research Institute of Experimental Medicine of Kursk State Medical University (KSMU), adhering to ethical principles for the handling of laboratory animals [11, 12]. The study was conducted in compliance with the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (CETS No. 123, as amended by ETS No. 170), GOST R 33647-2015 "Principles of Good Laboratory Practice (GLP), Terms and Definitions (as amended)" (Order of the Ministry of Health of the Russian Federation No. 199n of April 1, 2016), and GOST R 33216-2014 "Guidelines for the Care and Housing of Laboratory Animals. Rules for the Care and Housing of Laboratory Rodents and Rabbits (Reissue)".

The experimental protocol for this dissertation research was approved by the Regional Ethics Committee of KSMU (Minutes No. 4 of the Preclinical Research Section meeting of December 15, 2022).

Four groups of experimental animals were formed: 1) naïve – without the mandibular defect and metabolic syndrome ($n = 6$); 2) control – the simulation of the mandibular defect ($n = 33$); 3) metabolic syndrome – metabolic syndrome simulation ($n = 5$); 4) experimental – the simulation of metabolic syndrome and the mandibular defect ($n = 37$).

MS was simulated in the rats of groups 3 and 4 by replacing the standard feed with a high-fat, high-carbohydrate diet (HFHCD) consisting of a mixture of standard feed (65.75%) with the addition of animal fat (lard 17%), fructose (17%), cholesterol (0.25%) and drinking water with a 20% fructose solution (total caloric content 4,400 kcal/kg, 54% of energy from fat) for 12 weeks *ad libitum* at the first stage of the experiment (weeks 1–12) [13, 14]. Rats of the naïve and control groups (groups 1 and 2) received standard dry granulated feed complying with GOST 34566-2019 "Complete Compound Feeds for Laboratory Animals", as well as water *ad libitum* for 12 weeks. MS development was assessed by changes in body weight, concentration of glucose and triacylglycerides (TAG) in blood plasma, which were measured using standard kits (Vector-Best, Russia) "Glucose GOD" (cat. No. B-8056) and "Triglycerides" (cat. No. B-8322) on a BA-400 biochemical automatic analyzer (BioSystems, Spain)

in animals consuming HFHCD (groups 3 and 4), and compared to the rats of groups 1 and 2.

The mandibular defect was simulated in 37 rats of the experimental group (after 12 weeks of HFHCD administration) and 33 animals of the control group using the method developed by A.S. Grigoryan et al. at the second stage of experiment (13–16 weeks) [15]. A 3-mm-diameter perforation hole was formed with a portable drill in the body of the right lower jaw in the molar area (with cooling with normal saline) using chloralhydrate narcosis (at a dose of 400 mg/kg). Rats of groups 2 and 4 were administered ceftriaxone intramuscularly at a dose of 100 mg/kg of body weight once a day for 2 days to prevent complications. The operated rats of the fourth group consumed HFHCD until the withdrawal from the experiment. Three rats from the experimental group and one animal from the control group died after the surgery. Animals of groups 2 and 4 with the mandibular defects were sacrificed on day 7, 14, 21, and 28 after surgery by chloral hydrate overdose. Two rats of group 4 (experimental group) were revealed to have muscle tissue interposition in the area of the mandibular defect and were excluded from further experiment. Animals of groups 1 and 3 were sacrificed by chloral hydrate overdose on day 85 (12 weeks + 1 day) after the experiment beginning.

The levels of BMP-2 (catalog number SEA013Ra) and BMP-7 (catalog number SEA799Ra) in the blood plasma were determined by enzyme-linked immunosorbent assay (ELISA) using standard kits from Cloud-Clone Corp. (China) on a Lazurit automated ELISA analyzer (Dynex Technologies, USA) according to the included instructions in the animals of all groups.

Distribution normality was assessed using the Shapiro – Wilk test, and variance homogeneity was assessed using Levene's test for statistical analysis of the results. The data are presented as the median and interquartile range Me [Q_1; Q_3]. Statistical hypotheses were tested by pairwise comparison using the nonparametric Mann – Whitney U-test to detect statistically significant differences between groups and the Bonferroni correction to address the problem of multiple comparisons. Parameter differences were considered to be significant at $p < 0.025$. The use of nonparametric statistics was due to the small sample size, different distribution patterns in the variation series, and unequal variances in comparing groups. Statistical processing was performed using Statistica version 13 software.

RESULTS

Increased body weight, plasma glucose, and TAG levels were detected in Wistar rats of the experimental and MS groups compared to animals of the naïve and control groups ($p < 0.025$), which confirms MS development in the rats that received HFHCD for 12 weeks (Table 1).

Table 1

Dynamics of Body Weight, Glucose and Triacylglycerides Concentrations in Blood Plasma of Rats with and without Metabolic Syndrome, Me [Q_1; Q_3]

Group	Body weight, g		Glucose concentration, mmol/l		Triacylglyceride concentration, mmol/l	
	At the beginning of the experiment	At the end of the experiment (12 weeks after)	At the beginning of the experiment	At the end of the experiment (12 weeks after)	At the beginning of the experiment	At the end of the experiment (12 weeks after)
Naïve (n = 6)	215.0 [210.0; 225.0]	400.0 [385.0; 415.0]	3.7 [3.6; 3.8]	3.8 [3.6; 3.9	1.8 [1.8; 1.9]	1.9 [1.8; 1.9]
Control (n = 33)	220.0 [210.0; 225.0], ^{x}p = 0.3698	420.0 [390.0; 435.0], ^{x}p = 0.3115	3.8 [3.7; 3.9], ^{x}p = 0.3023	3.8 [3.7; 3.9], ^{x}p = 0.2844	1.7 [1.6; 1.8], ^{x}p = 0.2540	1.8 [1.7; 1.9], ^{x}p = 0.3023
Metabolic syndrome (n = 5)	215.0 [210.0; 220.0], ^{x}p = 1.00, $^{*}p$ = 0.6502	470.0 [460.0; 480.0] ^{x}*, ^{x}p = 0.0081, $^{*}p$ = 0.0004	3.8 [3.7; 3.9], ^{x}p = 0.6481, $^{*}p$ = 0.6043	5.8 [5.6; 5.9]^{x}*, ^{x}p = 0.0081, $^{*}p$ = 0.0004	1.8 [1.7; 1.8], ^{x}p = 0.3613 $^{*}p$ = 0.2900	3.9 [3.9; 4.1]^{x}*, ^{x}p = 0.0081, $^{*}p$ = 0.0004
Experimental (n = 37)	215.0 [210.0; 220.0], ^{x}p = 0.9163, ^{y}p = 0.8007, $^{*}p$ = 0.4791	485.0 [460.0; 510.0] ^{x}*, ^{x}p = 0.0002, ^{y}p = 0.3822, $^{*}p$ = 0.0001	3.8 [3.7; 3.9], ^{x}p = 0.2620 ^{y}p = 0.7413, $^{*}p$ = 0.8612	5.8 [5.6; 5.9]^{x}*, ^{x}p = 0.0001 ^{y}p = 0.7267, $^{*}p$ = 0.0001	1.8 [1.7; 1.8], ^{x}p = 0.1458, ^{y}p = 0.7857, $^{*}p$ = 0.4240	3.8 [3.7; 3.9]^{x*}, ^{x}p = 0.0001, ^{y}p = 0.1620, $^{*}p$ = 0.0001

$^{x}p < 0.025$ compared to the naïve group; $^{y}p < 0.025$ compared to the metabolic syndrome group; * $p < 0.025$ compared to control group.

MS simulation was accompanied by a significant increase in plasma BMP-2 and BMP-7 levels compared to the naïve group ($p = 0.0081$) (Table 2).

An increase in BMP-2 concentrations was detected in the rats of the control group compared to the naïve animals on day 7 of the experiment ($p = 0.0024$). The levels of both BMPs in this group decreased compared to day 7 ($p = 0.0009$) fourteen days after the simulation of the mandibular defect; however, both values were higher than in the rats of the naïve group ($p = 0.0024$).

A decrease in the concentration of the studied BMPs in rats of the control group was also observed on day 21 compared to the previous period of the experiment, but the content of BMP-2 and BMP-7 three weeks after the simulation of the mandibular defect was significantly higher than in the naïve group ($p = 0.0024$). The content of both BMPs in rats of the control group remained virtually unchanged on day 28 after the mandibular surgery compared to that on day 21, and it was significantly higher than in rats of the naïve group ($p = 0.0024$).

Table 2

Results of Measuring BMP-2 and BMP-7 Concentration in the Blood Plasma of the Rats of the Naïve Group, the Metabolic Syndrome Group, the Control Group (Mandibular Surgery), and the Experimental Group (Metabolic Syndrome + Mandibular Surgery), *Me* [Q_1; Q_3]

Group	Experiment period	BMP-2 concentration in blood plasma, pg/ml	BMP-7 concentration in blood plasma, pg/ml
Naïve ($n = 6$)		46.0 [45.0; 48.0]	43.5 [43.0; 45.0]
Metabolic syndrome ($n = 5$)		50.0 [49.0; 50.0]^x, $p = 0.0081$	49.0 [47.0; 49.0]^x, $p = 0.0081$
Control ($n = 8$)	day 7	182.0 [125.5; 257.5]^x, $p = 0.0024$	88.5 [76.5; 107.0]^x, $p = 0.0024$
	day 14	64.0 [62.0; 68.5]^{xz}, $^x p = 0.0024$, $^z p = 0.0009$	68.5 [65.5; 72.0]^{xz}, $^x p = 0.0024$, $^z p = 0.0009$
	day 21	51.5 [50.0; 57.0]^{xz}, $^x p = 0.0024$, $^z p = 0.0009$	57.0 [53.0; 60.5]^{xz}, $^x p = 0.0024$, $^z p = 0.0016$
	day 28	52.0 [51.5; 52.0]^x, $p = 0.0024$	55.0 [51.0; 56.5]^x, $p = 0.0024$
Experimental ($n = 8$)	day 7	84.0 [82.0; 92.0]^y*, $^y p = 0.0043$, $*p = 0.0009$	66.5 [61.0; 67.5]^y*, $^y p = 0.0043$, $*p = 0.0009$
	day 14	50.5 [50.0; 55.5]*, $*p = 0.0009$	54.0 [51.0; 55,5]^y*, $^y p = 0.0068$, $*p = 0.0009$
	day 21	51.5 [50.5; 53.5]	49.0 [49.0; 51.0]*, $*p = 0.0039$
	day 28	48.0 [47.0; 48.5]*, $*p = 0.0019$	49.5 [49.0; 51.0]*, $*p = 0.0209$

$^x p < 0.025$ compared to the naïve group; $^y p < 0.025$ compared to the metabolic syndrome group; * $p < 0.025$ compared to the control group; $^z p < 0.025$ compared to the previous experiment period in the group

The content of both BMPs on day 7 of the experiment was significantly higher in rats of the experimental group (MS + mandibular surgery) than in animals of the metabolic syndrome group ($p = 0.0043$). BMP-7 concentration alone was higher compared to the MS group ($p = 0.0068$) on day 14 after the mandibular defect simulation. BMP-2 and BMP-7 concentrations did not differ significantly from the same indices in the MS group on days 21–28 ($p > 0.05$).

It was established that the BMP-2 content was significantly lower in the rats of the experimental group on day 7 ($p = 0.0009$), day 14 ($p = 0.0009$), and day 28 of the experiment ($p = 0.0019$) compared to the control groups. A decrease in the BMP-7 concentration in animals of the experimental group was revealed at all stages of the experiment ($p = 0.0009–0.0029$) compared to the control group.

Thus, the study allowed to establish an increase in the concentration of BMP-2 and BMP-7 in the MS simulation in rats, as well as a decrease in the BMP content in the process of reparative osteogenesis in the case of the mandibular defect in animals with MS compared to the group without metabolic disorders.

DISCUSSION

The study demonstrated that the MS development is accompanied by increased BMP-2 and -7 plasma levels. This was likely due to the development of metainflammation in MS – a chronic, low-grade inflammation of adipose tissue manifested by increased plasma levels of proinflammatory interleukins (ILs): IL-1, IL-6, and TNFα – in both patients and rats with experimental MS [16, 17]. Proinflammatory ILs stimulate the BMP-producing cells activity, particularly platelets and endothelial cells [18].

An increase in the BMP-2 and BMP-7 content in the blood plasma during reparative osteogenesis in the rats of the control (throughout the experiment) and experimental (BMP-2 alone on day 7, BMP-7 on days 7–14) groups. However, this increase was less

pronounced at almost all stages of the experiment in MS animals. In our opinion, this is explained by the depletion of BMP reserves due to the metainflammation development in the osteopregenitor cells, platelets, and endothelial cells during reparative osteogenesis, as well as a decrease in the osteoblast number in the area of the mandibular defect in MS rats, as shown in our previous study [10].

Literature data on the effect of carbohydrate metabolism disorders on the BMP-2 content are contradictory. Simulation of streptozotocin-induced type 1 diabetes mellitus in Sprague-Dawley rats was accompanied by a decrease in the expression of BMP-2 mRNA in the tissue of the upper jaw [19]. In contrast, an increase in the expression of BMP-2 mRNA, BMP-7, and the type II BMP receptor in the aorta was revealed in mice with experimental type 1 diabetes mellitus [20]. The authors explain this effect by an increase in endothelin activity, which has a regulatory effect on BMP production. Enhanced BMP production by endothelial cells, which was previously shown in a study of BMP-4 secretion [21], may be one of the mechanisms explaining the increase in the blood plasma levels of BMP-2 and BMP-7 in experimental animals, as established in our study.

BMP-2 and BMP-7 play a key role in the osteoinductive process and have a stimulating effect on the osteogenic differentiation of mesenchymal stem cells (MSCs) [22]. It has been established that one of the biologically active substances stimulating the production of BMP-2 during reparative osteogenesis is fibroblast growth factor-21 (FGF-21). The study has shown an increase in BMP-dependent protein transcription, alkaline phosphatase activity, and bone matrix mineralization under the influence of FGF-21, which is associated with the Smad activation, but not with that of p44/42MAPK proteins [23]. The combined administration of FGF-21 and BMP-2 in a hydrogel has a stimulating effect on the osteogenic differentiation of mesenchymal stromal cells and vascular growth in newly formed bone [24].

It has previously been shown that high BMP concentrations promote the differentiation of MSCs into osteogenic cells, while low concentrations activate the formation of adipocytes from MSCs [3]. A significant increase in BMP-2 and -7 levels increase in the control group was observed on day 7 after the mandibular defect simulation, while these values were significantly lower in the rats of the experimental group. These data suggest that the slowdown in the development of newly formed bone tissue in MS rats, which we demonstrated previously [10], is explained by the insufficient effect of low BMP-2 and BMP-7 concentrations on osteogenic differentiation and the conversion of a certain proportion of MSCs into adipocytes, among other things.

It is known that BMP-2 interaction with specific type I receptors activates the MSCs conversion into adipocytes, and the activation of specific type II receptors stimulates the osteogenic MSC differentiation [3]. It is possible that the MS development is accompanied by an increase in type I receptors specific to BMP and a decrease in type II receptors, which disrupts the osteoblasts formation and slows down the formation of newly formed bone tissue in MS rats.

A stimulating effect of BMP-2 on angiogenesis during periodontal bone tissue regeneration has been established [25], which promotes the bone remodeling process in the control group of rats and explains low intensity of this process in the experimental group. BMP-2 and FGF-21 enhance the polarization of M2-phenotype macrophages, which immunomodulatory effect enhances osteogenic differentiation of stem cells during periodontal bone defect restoration [25].

CONCLUSION

This study demonstrated a statistically significant increase in BMP-2 and BMP-7 plasma levels in male Wistar MS rats. The analysis of the mandibular integrity restoration revealed a decrease in BMP-7 concentrations in the experimental group of rats throughout the experiment, and a decrease in BMP-2 concentrations on days 7, 14, and 28, compared to the control group. These data suggest that the decreased BMP-2 and BMP-7 plasma levels may be some of the mechanisms explaining the slowdown in reparative osteogenesis in MS rats. The results presented in this study support the administration of BMP-2 and BMP-7 analogs to stimulate the mandibular integrity restoration in MS.

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