EXPRESSION OF microRNA MIR146A IN THE BLOOD PLASMA OF RATS WITH OBESITY AND KNEE ARTHROSIS AFTER ADMINISTRATION OF DEXAMETHASONE

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MicroRNAs are resistant to RNases and are highly specific for various pathological conditions, particularly inflammation, allowing them to be considered inflammation biomarkers. They were detected in all body fluids, and miR146a plays a key role in the pathogenesis of inflammation. A total of 180 male white Wistar rats were selected for the study. All animals were 8–10 weeks old and weighed 200–250 grams. The animals were divided into five groups of 36 each. The first received saline solution intramuscularly, while the others underwent experimental modeling of obesity and knee arthrosis. The second group received 1.0 ml of saline solution intramuscularly, while the third, fourth, and fifth groups received dexamethasone at doses of 1 ng/ml, 10 ng/ml, and 100 ng/ml, respectively. Blood samples for the study were collected on days 3, 5, and 10. The obtained parameters were analyzed at the statistical significance level ($p < 0.05$). Increased miR146a levels were observed in animals in the second group compared to the others, due to the development of inflammation associated with obesity and concomitant gonarthrosis. In the third group, expression levels decreased slightly, remaining high. In the fourth group, with the use of 10 ng/ml dexamethasone, miR146a expression levels decreased most significantly on days 3 and 5. In the fifth group, virtually no changes were observed, with the parameter decreasing only slightly. The 10 ng/ml dexamethasone dose demonstrated the greatest efficacy during the experiment, possessing the greatest anti-inflammatory activity compared to the other doses.

Keywords: gonarthrosis, dexamethasone, microRNA, inflammation, rats, obesity, expression, miR146a

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Compliance with ethical standards: the study was approved by the Ethics Committee of the St. Luke's Lugansk State Medical University of the Russian Ministry of Health (protocol No 1 dated 23 September 2025). When working with laboratory animals, the conditions of care and experimentation were fully compliant with the standards of Order No. 199n of the Russian Ministry of Health "On Approval of the Rules of Good Laboratory Practice" 1, adhering to the principles of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes, and strictly adhering to the Directive of the European Parliament and of the Council of the European Union on the Protection of Animals used for Scientific Purposes.

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ЭКСПРЕССИЯ микроРНК MIR146A В ПЛАЗМЕ КРОВИ КРЫС С ОЖИРЕНИЕМ И АРТРОЗОМ КОЛЕННОГО СУСТАВА НА ФОНЕ ВВЕДЕНИЯ ДЕКСАМЕТАЗОНА

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МикроРНК не поддаются действию РНКаз и высокоспецифичны для различных патологических состояний, в частности воспаления, что позволило рассматривать их как биомаркеры данного патологического процесса. Обнаружить их удалось во всех жидкостях организма, в патогенезе воспаления ключевую роль играют микроРНК miR146a. Целью работы было определить уровень экспресии miR146a у крыс с гонартрозом, сочетанным ожирением и коррекцией дексаметазоном с целью разработки дальнейших патогенетических механизмов лечения остеоартроза. Для исследования отобрали 180 самцов белых крыс линии Вистар в возрасте 8–10 недель массой 200–250 г. Животные были разделены на пять групп по 36 в каждой: в первой группе вводили физиологический раствор хлорида натрия внутримышечно, остальным экспериментально смоделировано ожирение и артроз коленного сустава. Особям второй группы вводили 1,0 мл раствора хлорида натрия внутримышечно, третьей, четвертой и пятой — дексаметазон в дозе 1 нг/мл, 10 нг/мл и 100 нг/мл соответственно. Забор крови для проведения исследования проводили на 3, 5, 10 сутки. Полученные показатели исследовали при уровне статистической значимости ($p < 0,05$). Установлено повышение уровня miR146a у животных второй группы в сравнении с остальными, за счет развития воспаления на фоне ожирения и сопутствующего гонартроза. В третьей группе уровень экспрессии незначительно снижался, но оставался высоким. В четвертой группе на фоне применения 10 нг/мл дексаметазона уровень экспрессии miR-146a снижался максимально на 3 и 5 сутки. В пятой группе изменения практически отсутствовали, показатель снижался незначительно. Наибольшую эффективность в процессе эксперимента выявлена при дозе дексаметазона 10 нг/мл — она обладала набольшей противовоспалительной активностью по отношению к остальным.

Ключевые слова: гонартроз, дексаметазон, микроРНК, воспаление, ожирение, экспрессия, miR146a

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In 2008, Tewari et al. experimentally discovered the presence of some forms of microRNA in blood plasma in a stable form that excludes the influence of RNases, which served as the beginning of their study as biomarkers of the inflammatory process [1–5]. Stability is ensured by dysregulation of cellular expression of microRNA, which can be observed during infection; the cell is also capable of releasing some forms into the extracellular space. Further studies showed the presence of biomarkers not only in blood plasma, but also in saliva, urine, bile, breast milk and other body fluids [6]. Currently, there is data on specific changes in the microRNA expression profile in various pathological conditions, for example, in oncology, cardiovascular diseases, inflammation, aging, etc. [7–8]. Advances in understanding the relationships between various genes, their products, and environmental factors have highlighted the role of epigenetic variation, which involves changes in gene expression that do not affect DNA structure but can be transmitted across generations. There are three levels of epigenetic regulation: genomic (DNA methylation), proteomic (responsible for histone modification), and transcriptomic (RNA regulation). MicroRNA is a large class of small, non-coding RNA molecules, 18–25 nucleotides in length, that regulate gene expression through complementary interactions with the 3'-untranslated regions of mRNA, leading to RNA degradation or inhibition of translation processes [9].

Today, a large number of microRNAs are known that are specific to each pathological condition and enable early diagnosis for timely treatment. Recent data have shown that miR21 and miR146a microRNAs are involved in the pathogenesis of inflammatory diseases [10]. The role of miR146a in the regulation of the cell cycle, apoptosis, proliferation, and cell differentiation, as well as in the pathogenesis of infectious diseases, has been elucidated [11–13].

Over the past 10 years, microRNA markers have been discovered as specific factors in osteoarthritis and rheumatic diseases [14–18]. Detection of miR146a in synovial fluid and plasma in osteoarthritis is a potential diagnostic and prognostic marker [19]. Increased miR146a levels in blood plasma indicate the development and progression of gonarthrosis, which in the vast majority of cases is associated with excess body weight [20]. MiR146a is considered a marker of obesity and can influence its development and progression when elevated in blood plasma. Physical activity promotes weight loss, which reduces miR146a expression [21].

The use of nonsteroidal and steroidal anti-inflammatory drugs (e.g., celecoxib, ibuprofen, dexamethasone, methotrexate, etc.) in the treatment of gonarthrosis helps suppress the synthesis of proinflammatory cytokines and miR146a by increasing the expression of miR149-5p and miR-let-7c-5p [22, 23]. Among glucocorticosteroids for the treatment of inflammatory joint diseases, including osteoarthritis, one of the most frequently used drugs is dexamethasone [24]. A 2018 meta-analysis found that miR146a expression levels are higher in patients with rheumatoid arthritis and osteoarthritis than in healthy controls, as it serves as a regulator of the primary immune response and is involved in the pathogenesis of osteoarthritis [22]. The question of miR146a expression levels in obesity associated with osteoarthritis treated with glucocorticosteroids remains open.

Investigating miR146a expression levels in rats with obesity and osteoarthritis provides insight into the pathogenetic mechanisms of disease development and the development of optimal treatment regimens. The aim of this study was to develop a pathogenetic treatment regimen for osteoarthritis associated with obesity using dexamethasone, taking into account the level of miR146a expression, and to evaluate the effect of different doses of dexamethasone (1 ng/ml, 10 ng/ml, and 100 ng/ml) on the level of miR146a expression in rats with an experimental model of obesity and gonarthrosis.

METHODS

The experiment was conducted at the Ask-Health Research Center, Bulgaria, and the Leningrad State Medical University named after St. Luki" of the Ministry of Health of the Russian Federation.

For the experiment, 180 male Wistar albino laboratory rats, 8–10 weeks old, weighing 200–250 g, were selected. The animals were maintained in a vivarium at a temperature of 22 ± 2 °C and a 12-hour day/night cycle and nights with free access to water and food. The animals were randomly divided into 5 groups (n = 36). The first served as a control and received 1.0 ml of saline solution; the second (obese + gonarthrosis) received 1.0 ml of saline solution; the third, fourth, and fifth (obese + gonarthrosis) received 1.0 ng/ml, 10 ng/ml, and 100 ng/ml of dexamethasone solution, respectively.

Dexamethasone doses were selected based on the following: 1 ng/ml is a low dose, reflecting the minimum effective concentration to simulate a minimal anti-inflammatory effect without significant immunosuppression; 10 ng/ml is a therapeutic dose used to suppress cytokine-induced inflammation in rats; 100 ng/ml — a high dose was used to simulate a possible “paradoxical” effect with glucocorticoid overexposure. The dose range was selected to evaluate the dose-dependent responses of miR146a from minimal to supertherapeutic. Saline and dexamethasone were administered intramuscularly once daily for 10 days. On days 3, 5, and 10, blood was collected from the tail vein and centrifuged to obtain serum to determine the dynamics of miR146a expression. This scheme is fully consistent with previously published studies on modeling the anti-inflammatory effect of dexamethasone in laboratory rats [24]. Adverse effects of dexamethasone were assessed based on behavioral activity (open field test), body weight, the Lee index, coat and skin condition, and blood glucose levels (no significant dose-dependent adverse effects were observed with 1 and 10 ng/ml; signs of hyperglycemia and decreased activity were observed at 100 ng/ml, consistent with the known adverse effects of high doses of glucocorticosteroids).

Obesity in animals was modeled using a high-calorie diet supplemented with increased amounts of fat (45%), plant-based carbohydrates (35%), and animal-based carbohydrates (35%) for 8 weeks. The Li index was used to evaluate the result (Li = 1000 — (body weight (g)) / (length from the tip of the nose to the anus (cm)). The presence of obesity was indicated by an index of more than 310 and an increase in body weight by 25–40% compared to the initial value, which indicates a moderate degree of obesity [25]. Gonarthrosis was modeled according to the author's method by repeated damage to the articular cartilage using a minimally invasive method, followed by immobilization for 2–4 weeks using the author's device until reliable radiographic signs of arthrosis were achieved using a high-frequency portable dental X-ray machine Posdion Rextar X, 70 kV, Posdion, South Korea.

Determination of microRNA (miR146a) was performed by quantitative reverse transcription followed by polymerase chain reaction in real time. Serum was obtained by centrifugation of 1.0 ml of venous blood of rats obtained from the tail vein at 12,000 rpm for 15 minutes at 4 °C. The resulting samples were immediately frozen at –80 °C until analysis.

Total RNA was isolated using the miRNeasy Serum/Plasma Kit (Qiagen, Germany; No. 217184) according to the

Table 1. Dynamics of serum miR146a expression in rats in groups 1, 2, and 3 on days 3, 5, and 10

Indicator	miR146a			*p*		
Day	3	5	10	3	5	10
group 1, *n* = 36	0.97	0.97	1.03	0.07	0.03	0.07
group 2, *n* = 36	1.83	1.79	1.77	0.08	0.08	0.02
group 3, *n* = 36	1.47	1.52	1.51	0.05	0.05	0.05

Note: *p* — the root mean square error at a value level of 0,05.

manufacturer's protocol. Extraction efficiency was monitored by adding an external synthetic controller (cel-miR-39, Qiagen, Germany). RNA was purified on silica gel columns and eluted with 14 µl of RNase-free water. For cDNA synthesis, TaqMan™ MicroRNA Reverse Transcription Kit reagents (Applied Biosystems, Thermo Fisher Scientific, USA; No. 4366596) were used together with strain-specific TaqMan™ MicroRNA Assays primers (USA) for miR146a (#000468).

Quantitative PCR was performed in 96-well plates on a QuantStudio™ 5 Real-Time PCR System (Applied Biosystems, USA) using TaqMan™ Universal PCR Master Mix reagents, No. AmpErase UNG, USA, #4324018. U6 snRNA, whose expression level remained stable across all study groups, was used as reference RNA.

Three technical replicates were used for each reaction, and the Livak method (2^-ΔΔCt) was used to estimate relative miRNA expression.

Statistical Analysis of Results

After digital data collection, the mean and standard deviation were calculated. Statistical analysis was performed using one-way analysis of variance (ANOVA) in SPSS (v.16.0 for Windows, 2007; SPSS, Inc., Chicago, IL). Significant differences are indicated as $p < 0.05$; when calculating percentages, the data from the first group were taken as 100%. Box-and-whisker plots were used to check the unidimensionality of the distribution of results [26]. Statistical processing and the construction of diagrams and graphs were performed using the Statistica10 program.

RESULTS

This study revealed a correlation between miR146a microRNA expression and obesity, gonarthrosis, and dexamethasone use. In the body, miR146a is involved in the regulation of the immune response and inflammation by suppressing the latter. MiR146a leads to a decrease in the production of proinflammatory cytokines (IL-6, IL-8, and TNFα) and is actively involved in the regulation of T-cell differentiation and neuroinflammatory processes.

The study found an increase in miR146a in group II, suggesting the development of inflammation in the body caused by cytokines produced by adipocytes and as a result of the inflammation that triggers gonarthrosis. The use of dexamethasone in the experiment resulted in decreased plasma miR146a levels in all study groups, despite its long-term use as an anti-inflammatory agent for the treatment of gonarthrosis associated with excess body weight (Table 1).

The study found an increase in the miR146a index on day 3 in group 2 by 188.6% ($p < 0.05$), on day 5 by 184.5% ($p < 0.05$), on day 10 by 146.6% ($p < 0.05$), compared to group 1, which may represent the body's response to inflammation caused by obesity combined with gonarthrosis. In group 3, a decrease in the miR146a index was observed compared to group 2, but the index remained high. On day 3, miR146a increased by 151.1% ($p < 0.05$), while on day 5 the index increased by 156.7% ($p < 0.05$), after 10 days of the experiment, an increase of 146.6% ($p < 0.05$) was observed compared to group 1. When comparing the parameters of groups 1 and 3, an increase in miR146a levels by 151.5% ($p < 0.05$) was observed on day 3, on day 5 by 156.7% ($p < 0.05$), and on day 10 by 146.6% ($p < 0.05$).

Dynamic analysis of miR146a expression in group I revealed no increase on day 5, while on day 10 there was an increase of 106.1% ($p < 0.05$). In group 2, a decrease in miR146a by 2.2% ($p < 0.05$) was observed on day 5, and on day 10 the indicator decreased by 3.3% ($p < 0.05$) compared to day 3, and by 1.2% ($p < 0.05$) compared to day 5 of the experiment. In group 3, there was a 103.4% increase ($p < 0.05$) on Day 5 compared to Day 3, a 102.7% increase ($p < 0.05$) on Day 10 compared to Day 3, and a 0.7% decrease ($p < 0.05$) compared to Day 5.

Administration of 10 ng/ml dexamethasone had a more pronounced anti-inflammatory effect in group 3 compared to the others. The miR146a microRNA level was significantly higher than in group 1, but decreased relative to group 2 (Table 2).

Experimentally, an increase in the miR146a expression level was found on day 3 of the experiment by 112.3% ($p < 0.05$), on day 5 by 108.2% ($p < 0.05$), and on day 10 by 113.5% ($p < 0.05$) compared to group 1, which was statistically less than in group 2. When comparing the miR146a expression level in group IV with group 2, a decrease of 40.5% ($p < 0.05$) was found on day 3, 41.4% ($p < 0.05$) on day 5, and 39.9% ($p < 0.05$) on day 10.

Dynamic analysis of the indicator within group 4 reveals a clear trend toward a decrease in miR146a expression on Day 5 by 3.7% ($p < 0.05$) compared to Day 3. On Day 10, the level increased by 107.3% ($p < 0.05$) compared to Day 3, and by 111.4% ($p < 0.05$) compared to Day 5.

A different result was observed when the dexamethasone dose was increased to 100 ng/ml. The miR146a microRNA

Table 2. Dynamics of miR146a expression in rat serum in groups 1, 2, and 4 on Days 3, 5, and 10

Indicator	miR146a			*p*		
Day	3	5	10	3	5	10
group 1, *n* = 36	0.97	0.97	1.03	0.07	0.03	0.07
group 2, *n* = 36	1.83	1.79	1.77	0.08	0.08	0.02
group 3, *n* = 36	1.09	1.05	1.17	0.04	0.07	0.04

Note: *p* — the root mean square error at a value level of 0,05.

Table 3. Dynamics of miR146a expression indicators in rat serum in groups 1, 2, and 5 on Days 3, 5, and 10

Indicator	miR146a			*p*		
Day	3	5	10	3	5	10
group 1, *n* = 36	0.97	0.97	1.03	0.07	0.03	0.07
group 2, *n* = 36	1.83	1.79	1.77	0.08	0.08	0.02
group 3, *n* = 36	1.71	1.73	1.67	0.03	0.04	0.03

Note: *p* — the root mean square error at a value level of 0,05.

level was significantly higher than in group 1. Compared to group 2, the indicators differed slightly but were significantly lower (Table 3).

A significant increase in miR146a was observed in group 5 on day 3 by 176.2% ($p < 0.05$) compared to group 1. When studying microRNA in the blood plasma of group 5 on day 5, the indicator increased by 178.3% ($p < 0.05$) compared to group 1. On day 10 of the experiment, a significant increase in the miR146a concentration in group 5 by 159.2% ($p < 0.05$) was observed compared to group 1. When comparing the indicators of group 5 with group 3, a decrease in concentration was established against the background of dexamethasone administration: on day 3 by 6.6% ($p < 0.05$), on day 5 by 3.4% ($p < 0.05$), on day 10 by 5.7% ($p < 0.05$).

The dynamics of the parameter within group 5 showed a change in miR146a expression levels following dexamethasone administration. On Day 5, the parameter increased by 101.1% ($p < 0.05$) compared to Day 3, on Day 10, it decreased by 2.4% ($p < 0.05$) compared to Day 3, and by 3.5% ($p < 0.05$) compared to Day 5.

A visual representation of the dynamics of miR146a changes in blood plasma in all study groups can be presented using a graphical representation (Fig. 1).

DISCUSSION

The study revealed an increase in the miR146a microRNA concentration in the blood plasma of rats in all groups exposed to dexamethasone, compared to the control group. The highest level was observed in animals in group 2, indicating an inflammatory process caused by a group of cytokines secreted by adipocytes and the development and progression of gonarthrosis [27]. This is confirmed by an increase in miR146a expression in animals in group 3. Following administration of dexamethasone at a dose of 1 ng/ml, a decrease in miR146a expression was observed in animals in group 3 compared to group 2, indicating the anti-inflammatory properties of dexamethasone even at a low dose. The miR146a expression level in group 3 remained high compared to group 1, suggesting a low efficacy of 1 ng/ml dexamethasone on the studied parameter throughout the entire study period compared to a dose of 10 ng/ml [28].

In group 4, a more pronounced decrease in miR146a expression was observed with dexamethasone administration, which can also be explained by cytokine inhibition and suppression of inflammation caused by obesity and excess body weight [24]. The maximum result in this group was observed on day 5 of the experiment, which may indicate a cumulative effect of the drug due to its daily use or blockade of cellular receptors sensitive to cytokines [29]. On day 10, while the anti-inflammatory effect was maintained, miR146a expression levels increased slightly, which may be associated with decreased receptor sensitivity to the drug or its increased metabolism.

In group 5, no significant changes in miR146a levels were observed with dexamethasone administration compared to group 2, which supports the low efficacy of the 100 ng/ml dexamethasone dose throughout the entire experimental

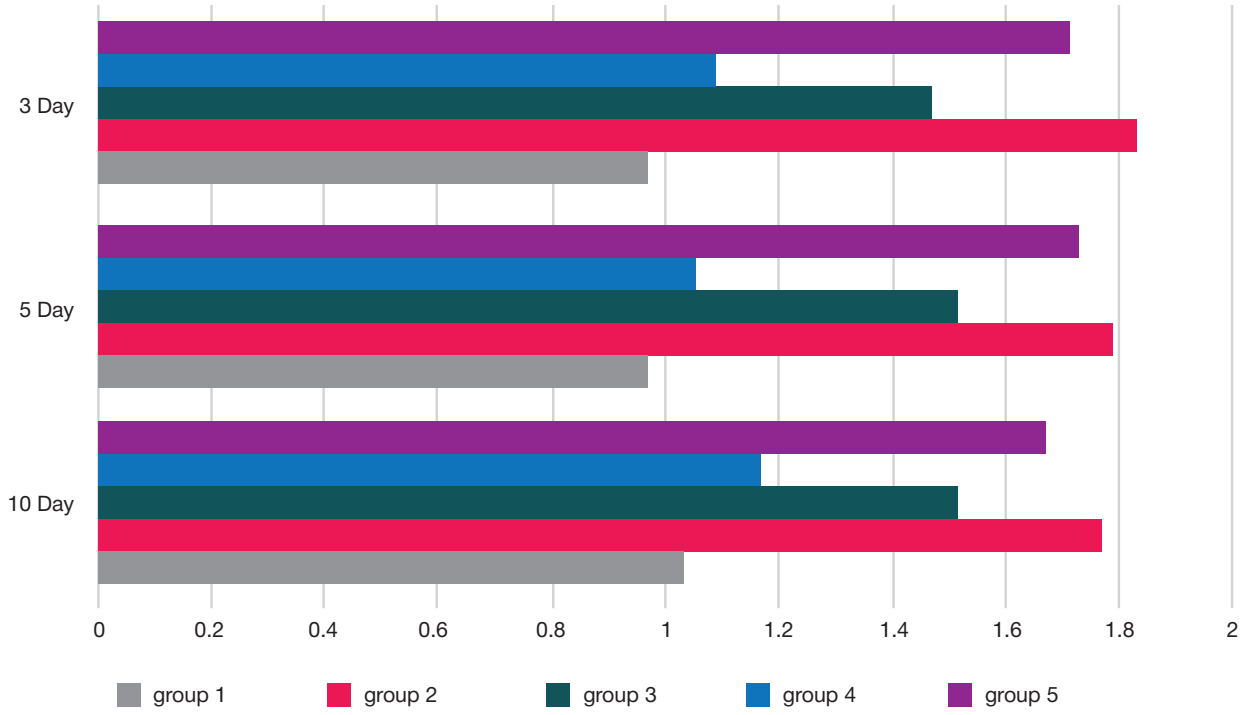

Fig. Dynamics of changes in the miR146a parameter in blood plasma of rats in groups 1, 2, 3, 4, and 5 on Days 3, 5 and 10

period. This may indicate the loss of dexamethasone receptors due to its high concentration or resistance to it at high doses, despite the drug's anti-inflammatory properties [30].

CONCLUSIONS

The study found that the maximum positive effect was achieved in group 4, as evidenced by a persistent and maximal reduction in miR146a expression. This circumstance allows us to recommend a dose of 10 ng/ml as a pathogenetically justified treatment for gonarthrosis associated with obesity over a long period of time. A minor positive effect from dexamethasone administration was observed in group III, as dexamethasone led to a decrease in miR146a expression; however, the level remained high compared to group 1. Dexamethasone at a dose of 1 ng/ml can be recommended as a pathogenetic therapy for pain syndrome or minor inflammation, as well as for the treatment of gonarthrosis not associated with obesity. It was found that a dose of 100 ng/ml dexamethasone was ineffective throughout the entire treatment period and did not significantly reduce miR146a expression in group V, which remained high, with minor fluctuations throughout the entire experimental period. Therefore, a dose-dependent effect of 100 mg dexamethasone on miR146a cannot be concluded and requires further clinical study. Potential for further research includes examining other plasma microRNA variants in patients with gonarthrosis associated with obesity, as well as blood glucose levels during dexamethasone treatment, dexamethasone receptor function, proinflammatory cytokine concentrations, and adrenal cortex function. Further study and titration of dexamethasone dose based on miR146a expression levels in clinical practice are of interest.

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