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Imbalance of vasoconstrictor / vasodilation potential caused by experimental osteoarthritis development

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Abstract

Study have been carried out on white Wistar line rats (age – 3 months, weight – 180-220 g). According to the tasks the animals were divided into 7 groups:

1st group is intact (n = 20). 2nd group is rats, which were modeled osteoarthritis without further correction and were withdrawn from the experiment in the first stage (7th day) (n=40). 3rd group is rats, which were modeled osteoarthritis without further correction and removed from the experiment in the second stage (21st day) (n=40). 4th group is rats, in which experimental osteoarthritis was corrected with nonsteroidal anti-inflammatory drugs (NSAIDs) (Diclofenac) and aminoguanidine and removed from the experiment in the first stage (7th day) (n=20). 5th group is rats, in which experimental osteoarthritis was corrected with NSAIDs (Diclofenac) and aminoguanidine and withdrawn from the experiment in the second stage (21st day) (n=20). 6th group is rats, where experimental osteoarthritis was corrected using NSAIDs and a 7% L-arginine solution and withdrawn from the experiment in the first stage (7th day) (n=20).

7th group is rats, in which experimental osteoarthritis was corrected with NSAIDs and 7% L-arginine solution and withdrawn from the experiment in the second stage (21st day) (n=20)

Animals were withdrawn from the experiment for the 7th day and the 21st day after the simulation of the pathological condition. NSAIDs (Diclofenac), aminoguanidine and L-arginine were administered from the beginning of the study.

As a research result was found significant increase in the endothelin-1 level in the blood, which indicates about imbalance endothelium functioning in the predominance direction of vasoconstrictor potential. Shift the balance towards vasoconstriction is evidence of the blood vessels vasodilating potential weakening.

There is a positive trend in the endothelial dysfunction correction in osteoarthritis with the aminoguadine administration. L-arginine effectiveness has been proven as a corrective agent for the endothelial function normalization in experimental osteoarthritis. It has been proven that use of nitric oxide donor are more effective than the use of an inducible NO synthase inhibitor.

Key words: osteoarthritis; experimental model; endothelial dysfunction; endothelin-1; aminoguanidine; L-arginine.

Introduction

According to the WHO, in the next 10-15 years, osteoarthritis (OA) will be the fourth cause of disability in women, and the eighth - in men [1]. At this stage, osteoarthritis is considered as a complex disease, in which in process involves all joint structural components [2, 3]. Several authors define OA as a heterogeneous diseases group of different etiology with identical clinical, morphological and biological manifestations, which are based on cartilage, subchondral bone, synovial membrane, ligament, capsule and paraartiular muscle damage [4, 5]. Recently, attention has been paid to endothelial pathology development in patients with OA [6]. Significant role in this aspect is given to chronic inflammation, as endothelial dysfunction trigger mechanism.

Oxidative stress [7, 8], endothelins production and endoperoxides, which are vasoconstrictors, are defined as causes of violation the functioning and endothelial vessels layer structure violation in osteoarthritis. Inflammatory cytokines that violate nitric oxide production [8, 9] also play a role.

Materials and methods

Study have been carried out on white Wistar line rats (age – 3 months, weight – 180-220 g). According to the tasks the animals were divided into 7 groups:

1st group is intact (n = 20).

2nd group is rats, which were modeled osteoarthritis without further correction and were withdrawn from the experiment in the first stage (7th day) (n=40).

3rd group is rats, which were modeled osteoarthritis without further correction and removed from the experiment in the second stage (21st day) (n=40).

4th group is rats, in which experimental osteoarthritis was corrected with nonsteroidal anti-inflammatory drugs (NSAIDs) (Diclofenac) and aminoguanidine and removed from the experiment in the first stage (7th day) (n=20)

5th group is rats, in which experimental osteoarthritis was corrected with NSAIDs (Diclofenac**)** and aminoguanidine and withdrawn from the experiment in the second stage (21st day) (n=20)

6th group is rats, where experimental osteoarthritis was corrected using NSAIDs and a 7% L-arginine solution and withdrawn from the experiment in the first stage (7th day) (n=20)

7th group is rats, in which experimental osteoarthritis was corrected with NSAIDs and 7% L-arginine solution and withdrawn from the experiment in the second stage (21st day) (n=20)

Animals were withdrawn from the experiment for the 7th day and the 21st day after the simulation of the pathological condition. NSAIDs (Diclofenac), aminoguanidine and L-arginine were administered from the beginning of the study.

Endothelin-1 which is an indicator of vasoconstrictor potential, its were determined by enzyme immunoassay (ELISA/EIA).

Aminoguadine is a selective inhibitor of inducible NO synthase (iNO-synthase), given to experimental animals at a dose of 15 mg/kg/day in the form of a solution in the free drink mode [10].

Nitric oxide donor administration a solution of L-arginine (SIMESTA, made in China, quality standard USP32) was carried out by intragastric injection of L-arginine solution in 0.9% sodium chloride solution at a dose of 500 mg / kg (Pokrovsky M.V., Pokrovskaya T.G., Korchakov V.I., etc., 2008) through a syringe with a feeding tube.

Both drugs were administered throughout the experiment.

Research was conducted in accordance with the "Rules for carrying out works using experimental animals", approved by the Order of the Ministry of Health of Ukraine No. 249

of 01.03.2012 and the Law of Ukraine No. 3447-IV "On the Protection of Animals from Cruel Treatment" (as amended on December 15, 2009, and 10/16/2012)

Destructive-dystrophic process of cartilage tissue was modeled by knee joint criodamadge**.** One-time intraarticular injection was performed with solution of cooled ethanol (Vvedensky BP, Galchenko SE, Kovalev GO, 2011).

Choice of this modeling method is justified by the fact that it does not require surgery, allows to standardize the experimental reproduction of the pathological process, reduces the risk of complications and does not lead to paraarticular tissues damage. This model provides a high frequency of consequences of local and general changes in the body in response to a modeled pathological process [11].

Before using parametric, normality-based statistical distribution methods, it were used to test the series of quantitative data for normality using the Shapiro–Wilk test. Due to the normal distribution of digital data in the samples, was used Student's parametric criterion.

Research results

Investigation of endothelin-1 dynamics against the background of experimental osteoarthritis and its correction (Table 1).

Table 1. Endothelin-1 dynamic level in the blood of rats during experimental osteoarthritis and its correction

Group	Intact	OA without correction I stage	OA without correction II stage	OA with NSAIDs correction and aminoguanidine I stage	OA with NSAIDs correction and aminoguanidine II stage	OA with NSAIDs correction and L-arginine I stage	OA with NSAIDs correction and L-arginine II stage
№ п/п	1	2	3	4	5	6	7
Endothelin-1	3,15±0,01	4,09±0,22 p_{21}<0,001	3,90±0,01 p_{31}<0,001 p_{32}=0,38	3,85±0,01 p_{41}<0,001 p_{42}=0,046	3,72±0,02 p_{51}<0,001 p_{54}<0,001 p_{53}<0,001	3,28±0,03 p_{61}=0,002 p_{62}<0,001 p_{64}<0,001	3,18±0,02 p_{71}=0,27 p_{76}=0,001 p_{73}<0,001 p_{75}<0,001

In determining this indicator has been established the predominance of the vasoconstrictor potential in the background of the development of experimental osteoarthritis. The endothelin-1 dynamics at the first stage of the experiment is presented in Fig.1.

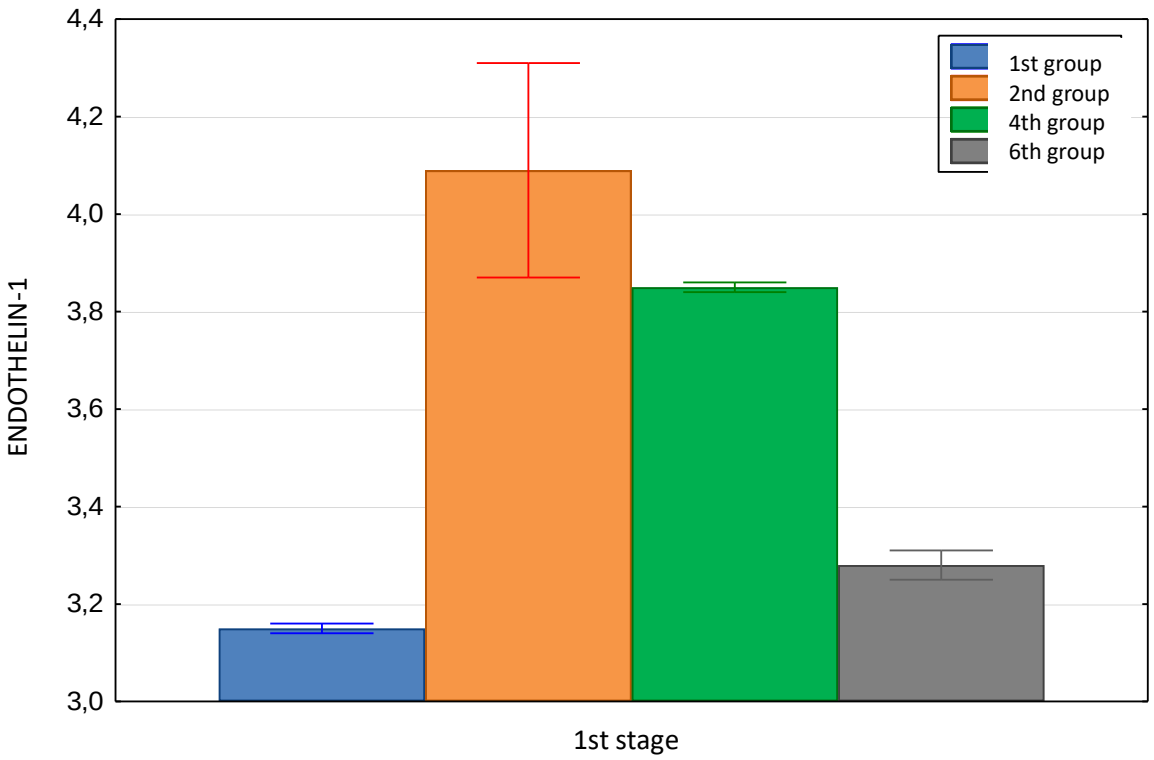

Figure 1 - Dynamics of endothelin-1 levels in the first stage of the experiment

It was found an increase in endothelin-1 levels in the group that did not correct experimental osteoarthritis by 29.8% in the first stage and by 23.8% in the second stage, this figure was higher than in intact animals.

When comparing this two methods of correction treatment, L-arginine was more effective, which is confirmed by the results presented in Table 1. Compared with the data of animals blood that were not corrected by the pathological process in the first stage, in the group with correction of NSAIDs the level of endothelin-1 decreased by 5.9%, while in the group, in which OA corrected NSAIDs and

L-arginine - by 19.8%.

At the second stage, a decrease in the marker of vasoconstriction in the group, which was received as part of the correction of aminoguanidine, was reduced by 4.6%, while in the group receiving L-arginine by 18.5%. In dynamics in groups with correction, which included a nitrogen oxide donor, positive dynamics was found in endothelin-1 levels ($p<0.001$) (Figure 3). The vasoconstriction studied marker dynamics in the second stage is presented in Fig.2.

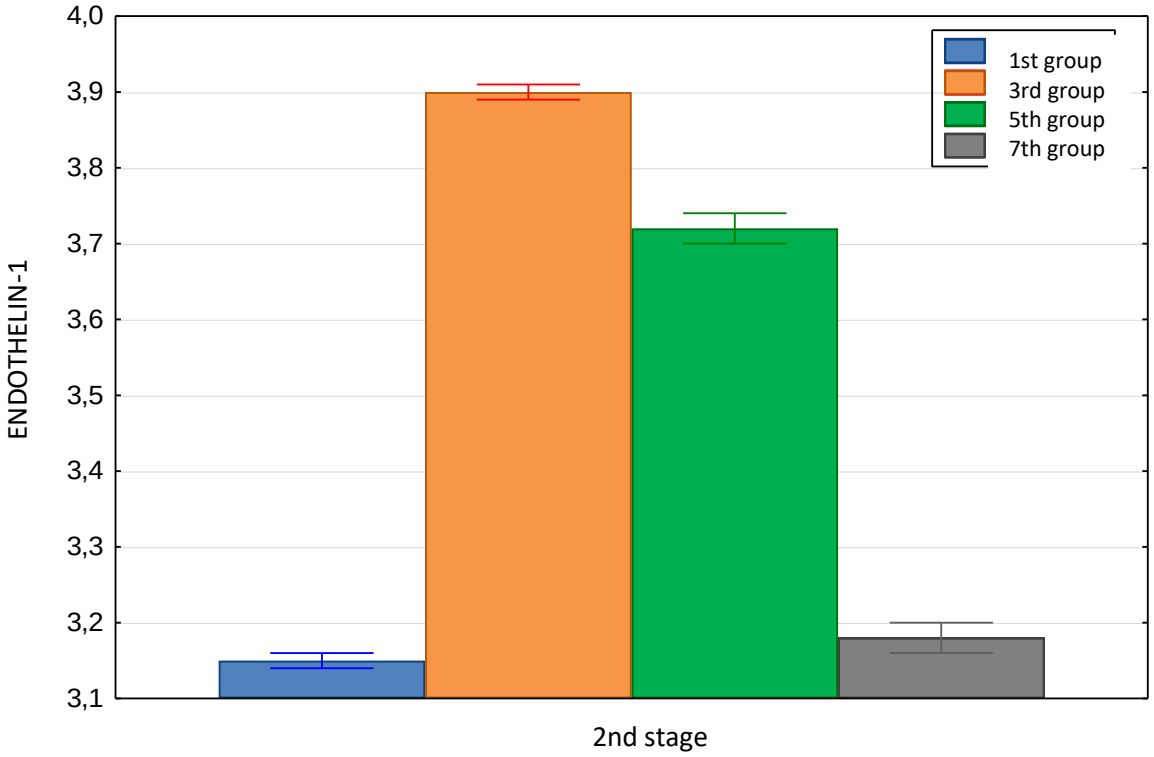

Figure 2 - Endothelin-1 levels dynamics in the second stage of the experiment

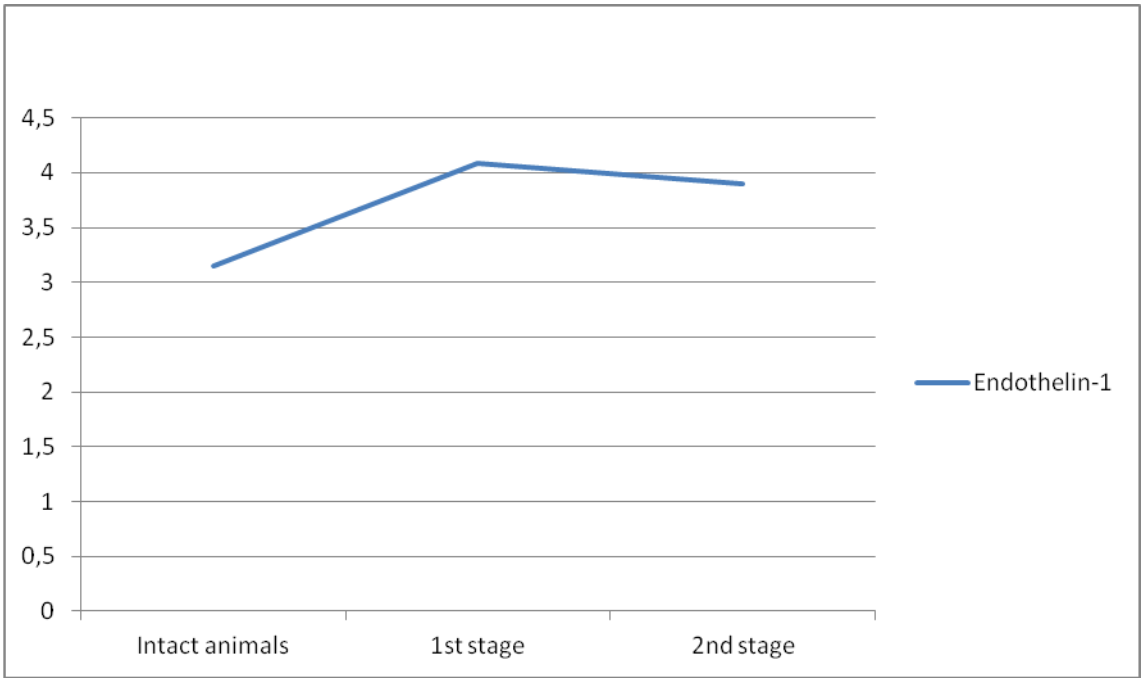

Figure 3 - Endothelin-1 level dynamic, which is endothelial dysfunction marker and vasoconstrictor potential, against the background of experimental osteoarthritis development

Conclusion:

1. As a research result was found significant increase in the endothelin-1 level in the blood, which indicates about imbalance endothelium functioning in the predominance direction of vasoconstrictor potential.

2. Shift the balance towards vasoconstriction is evidence of the blood vessels vasodilating potential weakening.

3. There is a positive trend in the endothelial dysfunction correction in osteoarthritis with the aminoguadine administration.

4. L-arginine effectiveness has been proven as a corrective agent for the endothelial function normalization in experimental osteoarthritis.

5. It has been proven that use of nitric oxide donor are more effective than the use of an inducible NO synthase inhibitor.

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