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Dynamic of changes in the level of Interleukin 1B against the background of the development of experimental diabetic retinopathy and under the influence of various methods of correction

Y. V. Sirman, I. V. Savytskyi, N. I. Preys, O. M. Blavatska

GE «Ukrainian Research Institute of Transport Medicine of the Ministry of Health of Ukraine»

Correspondence author: *Savytskyi Ivan Volodymyrovich, 65039, Odesa, Fountain road 4-a/29, tel.+38050-381-21-83, e-mail-farmakod@ukr.net*

Abstract

The aim of our research is investigating the changes in the level of interleukin 1β in experimental animals, which were simulated diabetic retinopathy and against the background of its correction. The obtained indicate that already on the 30th day of the development of experimental diabetic retinopathy, a significant increase in the pro-inflammatory cytokine level draws attention. Analyzing the data of group No. 3, it was established that the correction of the pathological condition with hypoglycemic agents has a positive effect but requires the involvement of additional means of correction in addition to the normalization of the level of glycemia. The results of the 4th experimental group indicate that the involvement of a nitric oxide donor and aflibercept in the correction of diabetic retinopathy has a positive effect on

the reduction of the level of Interleukin 1β, but it does not reach an approximation to the norm. It is observed that the correction of the simulated pathological condition by reducing hyperglycemia, administration of aflibercept and bromfenac (group No. 5) gives positive results, but less pronounced than involvement in the complex correction of L-arginine solution in the study of nitric oxide synthases, in the analysis of the pro-inflammatory cytokine level the results are better. It is also worth noting that this method of correction is not characterized by longevity and on the 180th day there is already a pronounced decrease in its effectiveness. It was found that in rats in which diabetic retinopathy was modeled with subsequent correction of hyperglycemia, administration of aflibercept, L-carnitine and bromfenac (group No. 6), there is a pronounced effectiveness of the proposed method of correction in comparison with the previously considered methods.

As for the correction applied in the 7th group, in the first and second stages, the inflammation indicator is more elevated compared to the two previous groups (No. 5 and No. 6), but in the third stage, a marked decrease in the level of the marker was established, which indicates the effectiveness of the correction of the 7th group at more distant stages of the experiment.

Keywords: experimental diabetic retinopathy; streptozotocin diabetes; inflammation; interleukin 1β; correction; metformin; aflibercept; bromfenac; L-carnitine; L-arginine; citicoline.

Introduction. According to the WHO, diabetic retinopathy (DR) is the main cause of vision loss and blindness in diabetes. This pathology is the main cause of visual impairment in the population of economically developed countries [1-4] and is diagnosed in 40-85 % of patients suffering from diabetes.

The informativeness of the study of the interleukin 1 β dynamics of in the pathogenesis of diabetes mellitus and DR is due to the fact that diabetic micro- and macroangiopathies are accompanied by hypoxia of endothelial cells and activation of macrophages that produce cytokines and, in particular, interleukins. At the same time, a "cytokine cascade" is formed, depending on the degree of hypoxia or reoxygenation, there is an imbalance in the ratio of pro- and anti-inflammatory mediators, and subsequent cell proliferation and apoptosis. All of the above determines the degree of inflammatory reaction, severity of free radical damage processes, cell death in the area of reduced blood supply [5]. Interleukin-1 is characterized by pro-inflammatory properties. It induces a significant part of local and general manifestations of inflammation. First of all, this happens due to an increase

in the adhesiveness of the endothelium of blood vessels for blood-forming elements and an increase in the procoagulant activity of cells. Interleukin-1 increases the mobility of neutrophils, promotes the activation of cells in the epicenter of inflammation, increases the production of prostaglandins, the synthesis of fibronectin and collagen, stimulates the production of superoxide radicals, phagocytosis and causes the degradation of mast cells. As a result, the exudative and proliferative component of the inflammatory reaction is formed [6, 7]. Under the influence of interleukin 1, vascular endotheliocytes produce polypeptides similar to platelet growth factor. They stimulate proliferation and cell migration and induce the release of vascular inflammatory mediators, leading to disseminated intravascular coagulation. An imbalance between endothelial vasodilators and vasoconstrictors in the direction of the latter during diabetes is also associated with a high content of cytokines, in particular Interleukin 1β, which indicates mediating damage to the vascular endothelium [6].

The aim of work – to investigate the changes in the level of interleukin 1β in experimental animals, which were simulated diabetic retinopathy and against the background of its correction.

Materials and methods. The study was conducted on white Wistar rats weighing 180-200 g. According to the tasks, the animals were divided into 7 groups:

1st group – intact animals;

2nd group – 60 animals with modelling of DR without correction (control pathology);

3rd group –60 animals with modelling of DR with correction of hyperglycemia;

4th group – 60 animals with modelling of DR with correction of hyperglycemia, administration of aflibercept and L-arginine solution;

5th group – 60 animals with modelling of DR with correction of hyperglycemia, administration of aflibercept and bromfenak;

6th group – 60 animals with modelling of DR with correction of hyperglycemia, administration of aflibercept, L-carnitine solution and bromfenak;

7th group – 60 animals with modelling of DR with correction of hyperglycemia, administration of aflibercept, L-arginine solution and citicoline.

Type 2 diabetes and DR were modeled by intraperitoneal administration of streptozotocin (Sigma, USA) dissolved in 0.1 M citrate buffer with pH 4.5 [14, 15]. Dose of streptozocin of 55 mg/kg of animal weight was divided into two administrations. Administration of streptozocin was preceded by a high-fat diet for 28 days [10].

Animals were subjected to research by decapitation in accordance with the "Rules for the performance of work 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 Cruelty" (as amended on 15.12.2009 and 16.10.2012).

The hypoglycemic medicine – metformin (Merck Sante, manufactured in France) - at at a dose of 300 mg/kg body weight [11] in a 0.9 % sodium chloride solution through a syringe with an intragastric probe daily, during the entire experiment.

The introduction of L-arginine solution, which is NO donor, (SIMESTA, manufactured in China, quality standard USP32) was carried out by intragastric administration of L-arginine solution in 0.9 % sodium chloride solution at a dose of 500 mg/kg [12] through a syringe with an intragastric probe.

Aflibercept (anti-VEGF therapy) was administered in the form of subconjunctival injections at a dose of 0.08 ml (25 mg/ml) [13] with an interval of 1 injection every 30 days.

Citicoline – 81.8 mg/kg (0.33 ml/kg) was administered intramuscularly once per a day [14].

Bromfenak – was introduced of 0,09 % eyes drop solution once per a day [15].

L-carnitine (manufacturing by “Sigma”, USA) was administrated in the form of an aqueous solution through a syringe with an intragastric probe at a dose of 25 mg/100 g of animal weight [16, 17].

The level of interleukin 1β was analyzed by the immunoenzymatic method using the "Vector BEST" kits.

To identify changes in the studied indicators between different groups and at different stages, we used parametric statistical methods, which are based on operating with the parameters of the statistical distribution (mean and variance). The methods used are designed for normally distributed data, so we checked all data for normality using E.I. Pustilnyk's asymmetry and kurtosis criterion. All the data that we are considering turned out to be normally distributed, so we can pairwise compare the mean values of the samples. Note that in the following comparisons we perform comparisons in independent samples. These will be comparisons between different groups of animals or comparisons between the same group of animals (but since there is no correspondence between animals in the samples, they will also be independent). The value $p<0.05$ was chosen as the reliability criterion. An analysis was performed to see if the means differed. The results of determining the t-test give an answer about the equality or difference of the mean values, but they do not provide an opportunity to accurately measure the difference between the mean values. Note that this difference is quite conditional. This difference was calculated as a percentage. Thus, we demonstrated a comparison of mean values between different groups of animals.

Results of study and their discussion:

The dynamics of the intelekin 1β level n the blood of experimental animals with simulated diabetic retinopathy and under the influence of various methods of its correction at each stage of the experiment are presented in Table 1.

There are no statistically significant differences in groups of intact animals, which indicates their homogeneity and suitability for further research and comparison. In the group of control athology without correction, at the first stage, a significant increase in the level of Interleukin-1 β was found compared to the data of intact rats – on 49.6 %. At the second stage, its level is higher on 56.7 % compared to the intact group and on 15.5 % compared to the data of its group at the previous stage. At the third stage, an even more pronounced increase of the studied marker is observed – its value is higher on 62.6 % compared to the 1st group, on 26.4 % more pronounced compared to its group at the 1st stage and on 12.9 % - on second.

In the third group, in which animals with simulated diabetes received metformin, the increase in the level of pro-inflammatory cytokine is less pronounced – on 15.07 % compared to group 2, but compared to group 1, it is greater on 68 %. At the second stage, the value of the indicator is lower on 21.8 % compared to the group without correction, but on 80 % it exceeds the data of intact animals, compared to the previous stage, the level increased on 8.9 %. In the third stage, the pro-inflammatory cytokine value is 18 % higher compared to the 1st stage and on 8.4 % higher compared to the 2nd stage. Its level is lower on 26.2 % than in the group without correction and compared to intact animals it is increased on 97 %. In the blood of rats of the 4th group, which received metformin, aflibercept and L-arginine solution against the background of simulated pathological process, the Interleukin 1 β level was less elevated on 23.9 % compared to the 2nd group and on 10.4 % compared to the 3rd group. Relative to group No. 1, it increased on 50.8 %. At the second stage of the experiment, the value of the indicator is 39.1 % higher than the data of intact animals, and compared to group No. 2 and No. 3, they are less elevated on 39.8 % and 22.9 %, respectively, and on 6.3 % lower compared to the 1st stage. At third stage, an even more pronounced positive trend was revealed – the level of the studied cytokine was on 12.4 % lower compared to the 1st stage and on 6.5 % lower than the on second stage. It is also lower than the 2nd and 3rd groups on 51.01 % and 33.6 %, respectively. But compared to the intact group, it is increased on 30.9 %.

Table 1 – The Interleukin 1β lebel in the blood of experimental animals with modelling diabetic retinopathy and its different methods of correction on the 30th, 60th and 180th day (M±m), (μM/l)

Stage Groups	I stage (A)		2 stage (B)		3 stage (C)	
Group 1	34,75±0,55		35,29±0,37		35,06±0,43	
	-	-	1A-1B	p>0,05	1A-1C 1B-1C	p>0,05 p>0,05
Group 2	68,91±0,42		81,52±0,52		93,66±0,44	
	1A-2A	p<0,001	1B-2B 2A-2B	p<0,001 p<0,001	1C-2C 2A-2C 2B-2C	p<0,001 p<0,001 p<0,001
Group 3	58,52±0,48		63,75±0,51		69,11±0,52	
	1A-3A 2A-3A	p<0,001 p<0,001	1B-3B 2B-3B 3A-3B	p<0,001 p<0,001 p<0,001	1C-3C 2C-3C 3A-3C 3B-3C	p<0,001 p<0,001 p<0,001 p<0,001
Group 4	52,4±0,51		49,09±0,46		45,88±0,35	
	1A-4A 2A-4A 3A-4A	p<0,001 p<0,001 p<0,001	1B-4B 2B-4B 3B-4B 4A-4B	p<0,001 p<0,001 p<0,001 p<0,001	1C-4C 2C-4C 3C-4C 4A-4C 4B-4C	p<0,001 p<0,001 p<0,001 p<0,001 p<0,001
Group 5	43,79±0,5		38,84±0,4		43,88±0,42	
	1A-5A 2A-5A 3A-5A 4A-5A	p<0,001 p<0,001 p<0,001 p<0,001	1B-5B 2B-5B 3B-5B 4B-5B 5A-5B	p<0,001 p<0,001 p<0,001 p<0,001 p<0,001	1C-5C 2C-5C 3C-5C 4C-5C 5A-5C 5B-5C	p<0,001 p<0,001 p<0,001 p<0,001 p>0,05 p<0,001
Group 6	39,88±0,39		35,97±0,45		38,24±0,51	
	1A-6A 2A-6A 3A-6A 4A-6A 5A-6A	p<0,001 p<0,001 p<0,001 p<0,001 p<0,001	1B-6B 2B-6B 3B-6B 4B-6B 5B-6B 6A-6B	p>0,05 p<0,001 p<0,001 p<0,001 p<0,001 p<0,001	1C-6C 2C-6C 3C-6C 4C-6C 5C-6C 6A-6C 6B-6C	p<0,001 p<0,001 p<0,001 p<0,001 p<0,001 p<0,05 p<0,01
Group 7	48,12±0,46		40,41±0,48		36,84±0,47	
	1A-7A 2A-7A 3A-7A 4A-7A 5A-7A 6A-7A	p<0,001 p<0,001 p<0,001 p<0,001 p<0,001 p<0,001	1B-7B 2B-7B 3B-7B 4B-7B 5B-7B 6B-7B 7A-7B	p<0,001 p<0,001 p<0,001 p<0,001 p<0,05 p<0,001 p<0,001	1C-7C 2C-7C 3C-7C 4C-7C 5C-7C 6C-7C 7A-7C 7B-7C	p<0,01 p<0,001 p<0,001 p<0,001 p<0,001 p>0,05 p<0,001 p<0,001

In the fifth group, in which the correction of simulated diabetic retinopathy was carried out with the help of metformin, aflibercept, and bromfenac, the effectiveness of the influence on the inflammatory process was monitored. Thus, at the first stage, the level of the studied indicator is on 36.4 % lower compared to second group, on 25.2 % compared to group No 3, and on 16.4 % compared to the 4th group. In the second stage, an even more pronounced normalization of the pathologically elevated marker is observed, it is on 11.3 % lower compared to the 1st stage, on 52.3 % lower compared to group No 2, on 39 % compared to group No. 3 and on 20.9 % compared to the 4th group. In comparison with the 1st group, it is increased on 10 %. But in the 3rd stage, the level of the marker increased again and on 12.9 % higher than in the 2nd stage and approaches the values of the 1st stage - the difference was only on 0.2 %. Compared to group No. 2, it is lower on 53 %, with group No. 3 – on 36.5 %, and with group No. 4 – on 4.3 %. Relative to the intact group, it is increased on 25%.

In the sixth group, in which diabetic retinopathy was modeled with subsequent correction of hyperglycemia, administration of aflibercept, L-carnitine and bromfenac, the tendency to normalize the level of pro-inflammatory cytokine is even more pronounced. Thus, at the 1st stage, its value is lower relative to the 2nd group on 42.1 %, relative to the 3rd on 31.8%, compared to the 4th on 23.9 %, and compared to the 5th on 8.9%. Compared to the intact group, the level is higher on 14.7 %. At the second stage of the experiment, the result is better on 9.8 % compared to the 1st stage. Relative to the 2nd, 3rd, 4th, and 5th groups, the level of Interleukin 1 β is less elevated on 55.8 %, 43.6 %, 26.72 %, and 7.4 %, respectively. In comparison with group No. 1, an increase only on 1.9 % was found. But in the 3rd stage, we again observe an increase in the level of the indicator: it is 6.3 % higher than in the 2nd stage, and only on 4 % less pronounced than in the 1st. Compared to the 2nd group, it is lower on 59.2 %, compared to the 3rd – on 44.6 %, compared to the 4th group - on 16.6 %, and compared to the 5th – on 12.8 %. Relative to intact animals, the level of the marker at this stage is on 9 % higher.

In the 7th group, in which the pathological condition was corrected by compensation of hyperglycemia, administration of aflibercept, a solution of L-arginine and citicoline in the first stage, the level of pro-inflammatory cytokine is on 30.2 % lower compared to group No. 2, on 17.8 % compared to group No. 3 and on 8.2 % lower compared to group No. 4. And relative to groups No. 5 and No. 6, it is more elevated on 9.9 % and on 20.7 %, respectively. In the second stage, the increase in the level of this marker is less pronounced compared to the previous stage – on 16 %, and on 50.4 %, on 36.6 % and on 17.7 % compared to the 2nd, 3rd and 4th groups respectively. Relative to the 5th and 6th groups, its value remains elevated, on

4 % compared to the 5th group and on 12.3 % compared to the 6th. At the 3rd stage, the level of the marker is less pronounced: on 60.7 % compared to group 2, on 46.7 % compared to the 3rd group, on 19.7 % compared to the 4th group, on 16 % compared to 5th group and on 3.7 % relative to the 6th group. Compared to the previous stages, it is lower on 23.4 % and on 8.83 %. That is, at the first and second stages, the inflammation indicator is more elevated compared to the two previous groups (No. 5 and No. 6), but at the third stage, a pronounced decrease in the level of the marker was established, which indicates the effectiveness of the correction of the 7th group at more distant stages of the experiment.

Conclusions:

1. The obtained indicate that already on the 30th day of the development of experimental diabetic retinopathy, a significant increase in the pro-inflammatory cytokine level draws attention.

2. Analyzing the data of group No. 3, it was established that the correction of the pathological condition with hypoglycemic agents has a positive effect, but requires the involvement of additional means of correction in addition to the normalization of the level of glycemia.

3. The results of the 4th experimental group indicate that the involvement of a nitric oxide donor and aflibercept in the correction of diabetic retinopathy has a positive effect on the reduction of the level of Interleukin 1β, but it does not reach an approximation to the norm.

4. It is observed that the correction of the simulated pathological condition by reducing hyperglycemia, administration of aflibercept and bromfenac (group No. 5) gives positive results, but less pronounced than involvement in the complex correction of L-arginine solution in the study of nitric oxide synthases, in the analysis of the pro-inflammatory cytokine level the results are better. It is also worth noting that this method of correction is not characterized by longevity and on the 180th day there is already a pronounced decrease in its effectiveness.

5. It was found that in rats in which diabetic retinopathy was modeled with subsequent correction of hyperglycemia, administration of aflibercept, L-carnitine and bromfenac (group No. 6), there is a pronounced effectiveness of the proposed method of correction in comparison with the previously considered methods.

6. As for the correction applied in the 7th group, in the first and second stages, the inflammation indicator is more elevated compared to the two previous groups (No. 5 and No.

6), but in the third stage, a marked decrease in the level of the marker was established, which indicates the effectiveness of the correction of the 7th group at more distant stages of the experiment.

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