DOI 10.26724/2079-8334-2021-4-78-203-208
UDC 616.379-008.64:611-018.74-092.9

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COGNITIVE DISORDERS EXPRESSION AND THEIR PATHOGENETIC CORRECTION IN THE DYNAMICS OF STREPTOZOTOCIN-INDUCED DIABETES

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Type 2 diabetes mellitus is becoming common disease and the most aggressive in terms of its onset in people of all ages. Understanding diabetes mellitus whole clinical picture complexity, associated primarily with its complications due to the complexity, cascade and versatility of "vicious circles" of disease pathogenetic mechanisms that cause both diabetic micro- and macroangiopathies formation, we attracted attention to the relationship 'diabetes vs cognitive disorders'. Chronic experimental trials were performed on Wistar rats using the model of streptozotocin-induced experimental diabetes mellitus. To correct the mnestic disorders we used metformin and alpha-lipoic acid separate and combined administration. The data obtained indicate the formation of cognitive disorders in streptozotocin-induced experimental diabetes mellitus dynamics which is confirmed by learning process failure as well as short- and long-term memory weakening. We revealed a pronounced reduction of amnestic reactions in animals after metformin and alpha-lipoic acid combined administration, which is manifested by the investigated mnestic parameters normalization. The proposed complex scheme of pharmacocorrection is effective, has a pathogenetic basis and a pronounced sanogenetic effect, which in the case of further detailed study might have clinical significance.

Key words: diabetes mellitus, training, short-term memory, long-term memory, conditioned reflexes, pathogenetic mechanisms, metformin, alpha-lipoic acid.

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ВИРАЖЕНІСТЬ КОГНІТИВНИХ РОЗЛАДІВ ТА ЇХ ПАТОГЕНЕТИЧНА КОРЕКЦІЯ В ДИНАМІЦІ СТРЕПТОЗОТОЦИН-ІНДУКОВАНОГО ЦУКРОВОГО ДІАБЕТУ

Цукровий діабет 2 типу стає все більш розповсюдженим захворюванням та найбільш агресивним з точки зору його дебюту в осіб різного віку. Розуміючи складність усієї клінічної картини цукрового діабету, пов'язану перш за все з ускладненнями захворювання через комплексність, каскадність та багатобічність «хибних кіл» патогенетичних механізмів захворювання, які спричиняють формування діабетичних мікро- та макроангіопатій, нашу увагу привернув зв'язок цукрового діабету та когнітивних розладів. Експериментальні дослідження були виконані в умовах хронічного експерименту на щурах лінії Вістар на моделі стрептозотоцин-спричиненого експериментального цукрового діабету. З метою корекції мнестичних розладів щурам окремо та сумісно вводили метформін та альфа-ліпоєву кислоту. Отримані результати свідчать про формування когнітивних розладів в динаміці формування стрептозотоцин-індукованого експериментального цукрового діабету, що підтверджується погіршенням процесу навчання, а також послабленням коротко- та довготривалої пам'яті. За умов сумісного введення метформіну та альфа-ліпоєвої кислоти щурам із стрептозотоцин-провокованим експериментальним цукровим діабетом, відбувається виражена редукція амнестичних проявів у тварин, що проявляється нормалізацією досліджуваних мнестичних показників. Запропонована комплексна схема фармакокорекції є ефективною, має патогенетичне підґрунтя та цілком виражений саногенетичний вплив, що в разі подальшого ретельного дослідження матиме клінічне значення.

Ключові слова: цукровий діабет, короткочасна пам'ять, довгочасна пам'ять умовні рефлекси, патогенетичні механізми, метформін, альфа-ліпоєва кислота.

The work is a fragment of the research project "Investigation of endothelial dysfunction in diabetes, the possibility and effectiveness of a new method of diabetes treating", state registration No. 0118U001852.

Type 2 diabetes mellitus (DM) is becoming an increasingly common disease and the most aggressive in terms of its onset in people of all ages. There are statistics on a significant prevalence of patients and, most threateningly, a significant increase in the age of its initiation: according to the WHO, approximately 425 million people aged 20 to 79 suffer from this disease, and there are preconditions for a significant increase in the number of patients with diabetes over the next 20–25 years to 629 million people [8]. It is known that over the past 40–45 years, the number of people suffering from diabetes has increased almost fourfold [2], which gives the WHO the opportunity to talk about the "creeping epidemic of diabetes" [3].

Understanding the complexity of the whole clinical picture of diabetes, associated primarily with complications of the disease due to the complexity, cascade and versatility of the "vicious circles" of pathogenetic mechanisms of the disease that cause the formation of diabetic micro- (retinopathy, nephropathy and polyneuropathy) and macroangiopathies, our attention was drawn by the possible connection between diabetes and cognitive disorders. In this regard, there is the WHO data for 35.6 million patients with cognitive disorders and dementia, including Alzheimer's disease in 2010 [9] with a risk of increasing the number of this group of patients to 115.4 million people in 2050 [7].

The leading social concept of life expectancy puts us in front of an increasing number of elderly people, which raises several problematic questions in terms of the problem of diabetes. On the one hand, there are data from clinical studies that convincingly show the leading role of diabetes in the formation of cognitive disorders [12, 13], while the risk of dementia in patients with diabetes is halved compared to the general population [13]. From the point of view of basic science, a probable explanation for this fact may be the progressive demyelination of nerve fibers in diabetes, the severity of which is directly dependent on the duration of the disease [11].

The purpose of the study was to investigate the exprtession of cognitive disorders in the dynamics of the experimental model of streptozotocin-induced diabetes mellitus, as well as the impact of comprehensive pharmacological treatment on the studied indicators. Functioning of short-and long-term memory due to the period of development of the conditioned reflex of active avoidance (CRAA) was used as a study criterion for cognitive function in rats.

Materials and methods. Experimental studies were performed in a chronic experiment on 55 Wistar rats weighing 180–25 g. Experimental diabetes mellitus (EDM) was modeled in rats by intraperitoneal (i.p.) administration of streptozotocin (STZ; "Serva", Germany, 60 mg/kg) dissolved in sodium citrate buffer (pH=4.5). EDM formation was verified on the 2nd day by blood glucose level determining using an indicator test strip ('One Touch', Germany). Only the rats with blood glucose concentration above 15 mmol/L were selected for further experiments.

Rats were observed for 6 weeks (this time interval is sufficient for experimental diabetic polyneuropathy development [10]) after which treatment was started. The following pharmacons were tested: metformin (MF; Santa Cruz Biotechnology, Inc., USA; 200 mg/kg, i.p.) and alpha-lipoic acid (ALA; "Farmak", Ukraine, 50 mg/kg, i.p.). These drugs were administered to rats with EDM starting at 7 weeks for a further 4 weeks (up to 10 weeks of the experiment) once a day, twice a week (the 2 and 5 days). The animals were randomized into 5 groups: 1 – intact rats (control); 2 – rats with EDM; 3 – EDM rats with MF; 4 – EDM rats with ALA; 5 – EDM rats with combined MF and ALA administration. There were 11 rats in each experimental group.

Experiments on CRAA reproduction and mnestic functions investigation were performed in a rectangular chamber (50 x 15 cm) with metal walls 40 cm high and a metal floor connected to an electric power source. The chamber was divided into 2 equal parts. 20W lamps were installed in each compartment. The light switch-in was used as a conditional stimulus (CS). An electric current (0.5-0.8 mA) given through a metal floor was considered to be an unconditional stimulus (US) [1].

Rats were allowed to examine the camera for 5 min with the door open and the light off. The training procedure consisted of sequentially applying electric current to rats while they were in the illuminated compartment of the chamber. The training continued until the animal reached 9 avoidances out of 10 consecutively used CS.

Memory preservation was checked after 24 hrs (short-term memory) and 7 days (long-term memory) in a similar way. This combination of CS and US was repeated until the animal reached 9 avoidances out of 10 consecutive CS uses.

As an integrative indicator of mnestic functions expression the *"preservation"* index was calculated [1].

The pharmacological compounds whose effects were studied were administered 30 min before the CRAA formation (the 1st day of the trial – the *learning process*), 30 min before the CRAA reproduction after 24hrs (the 2nd day of the trial – *short-term memory*) and 30 min before the CRAA reproduction in a week (the 8th day of the trial – *long-term memory*). Animals in the control group received saline in a similar volume in the same time intervals.

The data obtained were calculated statistically using one-way variant ANOVA parametric criterion accompanied by a post-hoc Newman-Keuls test. The minimum statistical probability was determined at $p<0.05$.

Results of the study and their discussion. The animals were first presented with a conditioned stimulus, and after 5 s – unconditional. After a series of electric shocks, the animal first froze and then tried to escape from the electric shocks. Initially, the control group rats needed 22-26 s to reach the goal, after which the running time was reduced. An advance reaction developed – after the presentation of a conditioned stimulus, the animal moved to the opposite side to receive electrical stimulation. Consolidation of the lead reaction was a criterion for the formation of CRAA.

Starting from the first week after the introduction of STZ, the number of combinations of US and CS required for the occurrence of CRAA was 27% more than in the control observations ($p<0.05$, table 1).

Later, from the 2nd till the 4th weeks of the experimental trials the investigated index of the training continued to be increased and was equal to 33.9±3.3 that was 30.9 % more pertaining the same index in the control observations ($p<0.01$). The studied index with the time of the pathological condition

reproduction progressively increased and reached maximum values at the 8th and the 10th weeks of the trial, respectively, 39.1±4.1 and 42.4±4.3, which significantly exceeded (on 45.2 % and 62.9 %, respectively) the analogous control values ($p<0.01$).

Table 1

Severity of the formation of the conditioned reaction of active avoidance of short-term and long-term memory in the dynamics of streptozotocin-induced diabetes mellitus

Experimental groups, compounds used, doses (mg/kg)	Number of CSS and CS combinations required for the emergence of CRAA		
	Training	Short-term memory	Long-term memory
1. Control	25.9±2.6	7.2±1.1	2.7±0.5
2. STZ, 2 days of trials	27.3±2.7	6.9±1.0	3.1±0.4
3. STZ, 1st week of trials	32.9±3.1 *	10.7±1.2 *	3.4±0.6
4. STZ, 2nd week of trials	33.1±3.2 *	10.4±1.1 *	3.3±0.4
5 STZ, 4th week of trials	33.9±3.3 **	10.7±1.5 *	3.5±0.4
6. STZ, 6th week of trials	34.7±3.2 *	11.4±1.3 *	3.8±0.7
7. STZ, 8th week of trials	37.6±3.6 **	15.2±1.7 **	5.4±0.6 *
7. STZ, 10th week of trials	42.4±4.3 **	17.1±1.9 **	9.7±1.1 **

Notes: * – $p<0.05$, ** – $p<0.01$ – significant differences of the studied indicators in comparison with those in the control group of animals (statistical criterion – one-variant ANOVA + Krushkal-Wallis)

During the 1st week of the trial only in the group of rats with MF and ALA combined administration the number of US and CS combinations required for CRAA was 16 % less than in rats with STZ-provoked EDM ($p<0.05$, table 2).

Table 2

Influence of MF and ALA separate and combined administration on the CRAA formation expression, short-term and long-term memory manifestations in rats with STZ-induced diabetes

Experimental groups, compounds used, doses (mg/kg)	Number of CSS and CS combinations required for the emergence of CRAA		
	Training	Short-term memory	Long-term memory
1. Control	25.9±2.6	7.2±1.1	2.7±0.5
1st week of the experiment			
2. STZ	32.9±3.1 *	10.7±1.2 *	3.4±0.6
3. STZ + MF	31.7±2.7	9.2±0.9	3.4±0.4
4. STZ + ALA	32.3±2.7	9.6±0.9	3.3±0.6
5. STZ + MF + ALA	27.6±2.3 #	7.9±0.7 #	3.2±0.4
6th week of the experiment			
6. STZ	34.7±3.2 *	11.4±1.3 *	3.8±0.7
7. STZ + MF	31.9±2.8	8.9±0.8	3.4±0.5
8. STZ + ALA	29.8±2.9	9.7±0.8	3.6±0.6
9. STZ + MF + ALA	28.1±2.4 #	7.8±0.8 #	3.2±0.6
7th week of the experiment			
10. STZ	36.7±3.4 **	13.7±1.5 **	4.2±0.7
11. STZ + MF	28.7±2.6	9.2±0.8	4.1±0.6
12. STZ + ALA	29.2±2.8	9.8±0.9	4.3±0.6
13. STZ + MF + ALA	27.3±2.6 #	7.9±0.8 #	4.1±0.5
8th week of the experiment			
14. STZ	37.6±3.6 **	15.2±1.7 **	5.4±0.6 *
15. STZ + MF	28.9±2.5 #	10.1±0.9 #	4.0±0.5
16. STZ + ALA	31.1±2.8	11.2±1.2	4.3±0.5
17. STZ + MF + ALA	27.1±2.6 #	8.3±0.8 #	3.2±0.4 #
9th week of the experiment			
18. STZ	39.1±4.1 **	16.3±1.7 **	8.9±0.9 **
19. STZ + MF	29.1±2.6 #	9.8±0.8 #	6.6±0.8
20. STZ + ALA	31.7±2.7	10.3±0.9 #	6.7±0.6
21. STZ + MF + ALA	27.4±2.7 #	7.9±0.9 #	4.9±0.5 ##
10th week of the experiment			
22. STZ	42.4±4.3 **	17.1±1.9 **	9.7±1.1 **
23. STZ + MF	28.7±2.7 #	9.4±0.8 #	5.8±0.6 #
24. STZ + ALA	29.2±2.9	10.3±0.9 #	4.9±0.6 #
25. STZ + MF + ALA	26.9±2.6 #	7.9±0.9 #	4.2±0.4 ##

Notes: * – $p<0.05$, ** – $p<0.01$ – significant differences of the studied indicators in comparison with those in the control group of animals; # – $p<0.05$, ## – $p<0.01$ – significant differences of the studied indicators in comparison with those in the group of animals with the introduction of STZ (statistical criterion – one-variant ANOVA + Krushkal-Wallis)

Similar results, which indicate a more pronounced correction of the learning process in diabetic rats under the influence of MF and ALA complex administration, were recorded during 6-10 weeks of the

experiment (p<0.05). The last week of the trials gave us 26.9±2.6 successful US and CS combinations which was comparable with the same control index (p>0.05) and was 1.6 times less pertaining the same index in diabetic rats on the 10th week of the experimental trials without the treatment (p<0.05).

One could see the both MF and ALA separate introduction during the experimental time interval mainly did not affect the value of the training index (p>0.05).

With the time of STZ-induced pathological condition reproduction, the number of combinations of US and CS required for the CRAA repeating a day after its development, gradually increased, being 1.5 times more on the 4th week of the trials pertaining the control index (p<0.05). The value of the studied index on the 6th week of the experimental trial was equal to 11.4±1.3 that was 58 % greater if compare with the analogous data in the control group (p<0.05). The data we received on the 10th week of EDM was 2.4 times more than the control indicator (p<0.01).

Both MF and ALA seperate adminsitartions to diabetic rats were indifferent to the investigated indexes during the 8 weeks of the experimental trials. Their efficacy was evident on the 9th and the 10th weeks of the trials which was proved by their indexes significantly less pertaining the control data in diabetic rats on the 9th and the 10th weeks of the trials without the treatment (p<0.05).

Combined MF and ALA injection resulted in the short-term memory restoration in diabetic rats even at the end of the 1st week of the trials (p<0.05). The investigated indexes of the short-term memory functioning in diabetic rats under the influence of MF and ALA combined administration were steadily lower pertaining the same indexes in the correspondent control observations in diabetic rats without the treatment. Thus, on the 10th week of the trial the investigated index was equal to 7.9±0.9 that was comparable with the same index in the control rats (p>0.05) and was 2.2 times less pertatining the same index in diabetic rats without the treatment (p<0.05).

Under the influence of STZ in conditions of the EDM model there was a gradual increase in the number of US and CS combinations required for the emergence of CRAA 7 days after conditioned reflex development. These data indicated a marked long-term memory deterioration which became statistically probable at 8 week of trials (p<0.05). This investigated index maximal increase (9.7±1.1) - on 3.6 times (p<0.01) – we registered on the 10th week of the EDM.

Single MF and ALA adminsitartions failed to normalize long-term memory throughout 9 weeks of the experimentral trials. The investigated indexes on the 10th week of the model were equal to 5.8±0.6 and 4.9±0.6 that were on 40.2 % and 49.5 % less (p<0,05 in both cases), correspondently, comparing the same index in diabetic rats without the treatment.

At the same time, long-term memory was normalized under the influence of MF and ALA combined, starting from the 8th week of the trials (p<0.05), which persisted until the end of the experiment. The investigated index on the 9th week of EDM was equal to 4.9±0.5 that was on 44.9 % less (p<0,05) being compared with the same index in diabetic rats without the treatment. At the 10th week of the study, the number of US and CS combinationa required for CRAA emergence after 7 days from conditioned reflex development, was 2.3 times less than the corresponding index in the control measurements (p<0.01).

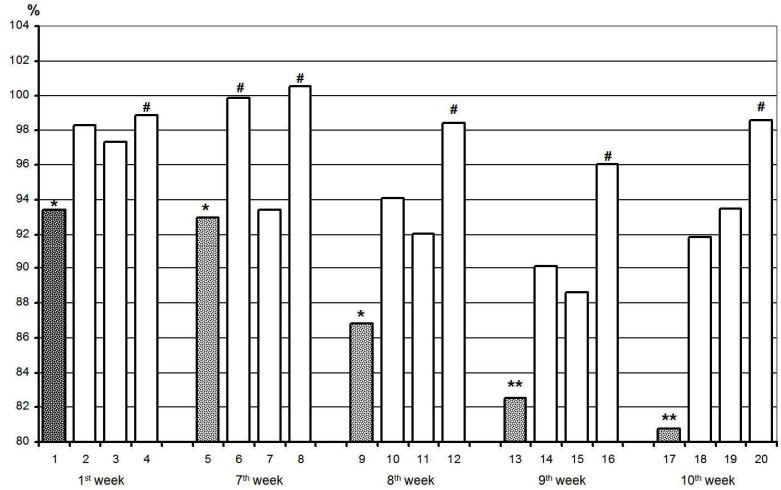

Fig. 1. The effect of separate and combined effects of MF and ALA on the index of "preservation" in rats with STZ-induced EDM Symbols: on the abscissa – 1 (5, 9, 13, 17) – rats with diabetes; 2 (6, 10, 14, 18) rats with diabetes + MF; 3 (7, 11, 15, 19) rats with diabetes + ALA; 4 (8, 12, 16, 20) rats with diabetes + MF + ALA. On the y-axis – the value of the studied indicator, expressed in % related to the same indicators in rats of control groups, taken as 100%.

Notes: * – p<0.05, ** – p<0.01 – significant differences of the studied indicators in comparison with those in the control group of animals; # – p<0.05 – significant differences of the studied parameters in comparison with those in rats with STZ-induced EDM, marked with dark bars (one-variant ANOVA + Krushkal-Wallis).

The relative values of the integral indicator of "preservation", which allowed us to assess the impact of the compound on the preservation of the skill (“engram”), are given in the figure. The value of “preservation” under the influence of co-administration of MF and ALA was significantly greater than in the control, starting from the 7th week of the trial (p<0.05, fig. 1).

At the 9th of the experiment, the value of the studied indicator was 14.1 % higher than in the control measurements (p<0.05). At the 10th week of EDM the incestigated index was 18.1 % less if compared with the control data(p<0.05). There is a tendency to increase the value of the indicator of “preservation”

depending on the term of complex pharmacological correction of cognitive disorders under the conditions of EDM.

Thus, the obtained results indicate the undoubted formation of cognitive disorders in the dynamics of the formation of STZ-induced EDM. This is confirmed in our studies by data on the deterioration of the learning process, as well as a pronounced weakening of short- and long-term memory within 10 weeks after the introduction of STZ. The obtained data are correlated with the results of studies [13], which showed the dynamics of deterioration of neurological processes in diabetes under experimental conditions and in the clinic. We consider the actual data obtained as a result of demyelination of nerve fibers, which begin to form in 1.5–2 months of diabetes due to a combination of endothelial dysfunction and alternative action of oxygen components, the accumulation of which is shown in the pathogenesis of diabetes [5, 11].

That is, the amnestic effect found by us in the dynamics of formation of STZ-induced EDM is confirmed by time-dependent inhibition of the process of conditioned reflex formation in the CRAA test, as well as deterioration of short- and long-term memory. Deterioration of the relative rate of "preservation" also reflects the negative neuropathophysiological processes that continue in the body of rats under the conditions of EDM.

Another significant block of data obtained indicates some positive aspects related to the prospect of recovery of mnestic disorders characteristic of EDM through the complex use of the classic antidiabetic drugs such as MF and ALA, which is characterized by antioxidant, membraneotropic properties and the ability to improve blood rheology [3, 6]. We consider the obtained results of a much more pronounced recovery of learning processes, indicators of short- and long-term memory, as well as the indicator of "preservation" to be an experimental substantiation of a correctly formulated and proposed scheme of pharmacological correction of cognitive disorders in EDM. Note that even in such a limited form, the selected complex scheme of pharmacological correction is effective while also having a pathogenetic basis and a pronounced sanogenetic effect..

Conclusions

1. In the dynamics of formation of STZ-induced EDM cognitive disorders are formed, which are manifested by inhibition of the learning process during the development of CRAA, deterioration of short- and long-term memory and deterioration of the relative indicator of "preservation".

2. Amnestic manifestations are progressive and are determined by the development of diabetes. The greater degree of their severity is registered within 6-10 weeks from the moment of reproduction of STZ-induced EDM, which coincides with the term of development of nerve fiber demyelination.

3. Under the conditions of joint administration of MF and ALA to rats with STZ-provoked EDM there is a pronounced reduction of amnestic manifestations in animals, which is manifested by the normalization of the studied indicators of learning, short-, long-term memory and "preservation".

4. Significant recovery of learning processes, indicators of short- and long-term memory, as well as the indicator of "preservation" is considered an experimental justification of a correctly formulated and proposed scheme of pharmacological correction of cognitive disorders in EDM.

Prospects for furthers researches include a detailed study of the effectiveness of the proposed scheme of pathogenetically based correction of cognitive impairment in type 2 diabetes with an emphasis on the developed scheme composition, dosages and its complexity to obtain convincing evidences of its clinical testing reasonability.

References

1. Buresh Ya, Byreshova O, H'juston D. Metodiki i osnovnyie ekcnerimenty no izycheniyu mozga i povedeniya. Moskva: Vyicshaya shkola, 1991: 400 [In Russian].

2. Areosa Sastre A, Vernooij RW, Gonzalez-Colaco Harmand M, Martinez G. Effect of the treatment of Type 2 diabetes mellitus on the development of cognitive impairment and dementia. Cochrane Database Syst Rev. 2017; 6:CD003804. doi: 10.1002/14651858.CD003804.pub2

3. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021; 44 (9): 15–33: doi: 10.2337/dc21-ad09

4. Corrêa LBNS, da Costa CAS, Ribas JAS, Boaventura GT, Chagas MA. Antioxidant action of alpha lipoic acid on the testis and epididymis of diabetic rats: morphological, sperm and immunohistochemical evaluation. Int Braz J Urol. 2019; 45(4): 815–824. doi: 10.1590/S1677-5538.IBJU.2018.0774

5. Daios S, Kaiafa G, Pilalas D, Nakou I, Kanellos I, Kirdas K, Despoudi K, Papanas N, Savopoulos C. Endothelial Dysfunction and Platelet Hyperaggregation in Type 2 Diabetes Mellitus: The Era of Novel Anti-diabetic Agents. Curr Med Chem. 2021; 28(20): 3935–3963. doi: 10.2174/0929867327666201009143816.

6. El Midaoui A, Fantus IG, Ait Boughrous A, Couture R. Beneficial Effects of Alpha-Lipoic Acid on Hypertension, Visceral Obesity, UCP-1 Expression and Oxidative Stress in Zucker Diabetic Fatty Rats. Antioxidants (Basel). 2019; 8(12): 648. doi: 10.3390/antiox8120648.

7. Hugo J, Ganguli M. Dementia and Cognitive Impairment: Epidemiology, Diagnosis, and Treatment. Clin Geriatr Med. 2014; 30(3): 421–442. doi:10.1016/j.cger.2014.04.001.

8. International Diabetes Federation. IDF Diabetes Atlas. 8th ed. Brussels: IDF, 2017: 124

9. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Dement. 2013; 9: 63–75
10. Vinik AI, Park TS, Stansberry KB, Pittenger GL. Diabetic neuropathies. Diabetologia. 2000; 43 (8): 957–973. DOI: 10.1007/s001250051477
11. Wagner R, Heni M, Tabák AG, Machann J, Schick F, Randrianarisoa E, Hrabě de Angelis M, Birkenfeld AL, Stefan N, Peter A, Häring H-U, Fritsche A. Pathophysiology-based subphenotyping of individuals at elevated risk for type 2 diabetes. Nat Med. 2021; 27(1): 49–57. doi: 10.1038/s41591-020-1116-9.
12. Wodschow HZ, Jensen NJ, Nilsson MSDD, Rungby J. The effect of hyper- and hypoglycaemia on cognition and development of dementia for patients with diabetes mellitus type 2. Ugeskr Laeger. 2018; 180(51):V08180566.
13. Wu C-Y, Ouk M, Wong YY, Anita NZ, Edwards JD, Yang P, Shah BR, Herrmann N, Lanctôt KL, Kapral MK, MacIntosh BJ, Rabin JS, Black SE, Swardfager W. Relationships between memory decline and the use of metformin or DPP_4 inhibitors in people with type 2 diabetes with normal cognition or Alzheimer's disease, and the role APOE carrier status. Alzheimers Dement. 2020; 16(12): 1663–1673. doi: 10.1002/alz.12161.

Стаття надійшла24.12.2020 р.

DOI 10.26724/2079-8334-2021-4-78-208-213
UDC 616.233+616.24]-002-097:575.117

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EXPRESSION OF ANGIOTENSIN-CONVERTING ENZYME-2 IN LUNG TISSUES IN EXPERIMENTAL BRONCHOPNEUMMONIA

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The purpose of this study was to establish the effect of acute pulmonary inflammation of non-viral origin on the expression of angiotensin-converting enzyme-2. Wistar rats (n=20) were introduced into the trachea of sterile nylon thread 2.5 cm long and 0.2 mm thick to a depth of 2.5 cm. Endotracheal injection of nylon thread led to formation of acute bronchopneumonia, which included the sequential development of: exudative and proliferative inflammation, peribronchial and alveolar abscesses, their organization and diffuse fibrosis of the lung parenchyma. It was shown that the exudative phase of acute inflammation was accompanied by inhibition of angiotensin-converting enzyme-2 expression in bronchial epitheliocytes, type II alveolocytes and vascular endothelium. During the transition of inflammation to the stage of proliferation and fibrosis, the expression of the enzyme was restored. The identified changes indicated the presence of regulatory factors that differ from the coronavirus action.

Key words: acute inflammation, fibrosis, endotracheal injection, immunohistochemistry

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ЕКСПРЕСІЯ АНГІОТЕНЗИН-ПЕРЕТВОРЮЮЧОГО ФЕРМЕНТУ-2 У ТКАНИНАХ ЛЕГЕНЬ ПРИ ЕКСПЕРИМЕНТАЛЬНІЙ БРОНХОПНЕВМОНІЇ

Метою дослідження було встановлення впливу гострого легеневого запалення не вірусного генезу на експресію ангіотензин-перетворюючого ферменту-2. Щурам лінії Вістар (n=20) було проведене введення у трахею стерильної капронової нитки довжиною 2,5 см та товщиною 0,2 мм на глибину 2,5 см. Ендотрахеальне введення капронової нитки призводило до формування гострої бронхопневмонії, яке включало послідовний розвиток: ексудативного і проліферативного запалення, перибронхіальних та альвеолярних абсцесів, їх організацію та дифузний фіброз паренхіми легень. Показано, що ексудативна фаза гострого запалення супроводжувалася пригніченням експресії ангіотензин-перетворюючого ферменту-2 у епітеліоцитах бронхів, альвеолоцитах II порядку та судинному ендотелії. При переході запалення у стадію проліферації та фіброзування експресія ферменту відновлювалася. Виявлені зміни вказували на наявність факторів регуляції, які відрізняються від дії коронавірусу.

Ключові слова: гостре запалення, фіброз, ендотрахеальне введення, імуногістохімія

The work is a fragment of the research project "Study of cell-molecular mechanisms of pharmacological influence on the reprogramming of the macrophages functional phenotype in wound regeneration on the background of hyperglycemia",state registration No. 0119U101219

Coronavirus disease 2019 (COVID-19) remains a serious threat to public health both today and in the future [15]. Coronavirus damages almost all systems and organs, but the lungs are most affected. Already at an early stage of the disease develops acute lung injury, which can lead to acute respiratory distress syndrome (ARDS) [13]. The exudative stage progresses to proliferative stage and pulmonary fibrosis [13].

After the first COVID epidemic in 2002, the functional receptor required for coronavirus to enter host cells was identified, they found angiotensin-converting enzyme-2 (ACE2) [8, 9]. In addition to lung