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To the editorial board of World Journal of Diabetes

By this letter, we confirmed that the manuscript titled **"Pathological changes in the cellular structures of retina and choroidea in the early stages of alloxan-induced diabetes"** by Irina Danilova, Svetlana Medvedeva, Svetlana Shmakova, Margarita Chereshneva, Petr Sarapultsev, Alexey Sarapultsev was performed within research work "The search of ways of pharmacological correction regenerative processes in the experimental model of diabetes" Project Number: 16-15-00039 of RUSSIAN SCIENCE FOUNDATION with project lead *Irina Danilova*.

Deputy director for Science
Institute of Immunology and Physiology of RAS
Ekaterinburg

Danilova IG

11.01. 2018

Project Finder

INFORMATION ABOUT PROJECT,
SUPPORTED BY RUSSIAN SCIENCE FOUNDATION

COMMON PART

Project Number: 16-15-00039

Project title: The search of ways of pharmacological correction regenerative processes in the experimental model of diabetes.

Project Lead: Danilova Irina

Affiliation: Federal State Autonomous Educational Institution of Higher Education "Ural Federal University named after the First President of Russia B.N. Yeltsin",

Implementation period: 2016 - 2018

Research area: 05 - FUNDAMENTAL RESEARCH IN MEDICINE, 05-101 - Experimental medicine

Keywords: Diabetes mellitus, pancreas, regeneration, antioxidants, thiadiazine, immunomodulators

PROJECT CONTENT

Annotation:

The project aims at development of new approaches to prevention and treatment of diabetes through search and synthesis of new chemical compounds that have antidiabetic effects, the justification of the mechanism of their action at the cell, tissue, organ and whole organism level.

Diabetes type 1 is a disease mainly of persons of working age, which leads to the disability of population. Difficulty of glycemic indices typical for healthy individuals achieving leads to the chronic complications of the disease progression. Hyperglycemia in diabetes causes the activation of oxidative stress, non-enzymatic glycosylation of proteins and secretion of proinflammatory cytokines by producer cells, which contributes to diabetes complications. Mechanisms of autoimmune aggression determining the manifestation and progression of the disease remain deprived of their pharmacological correction.

In this regard, attention is attracted to chemical compounds that combine the ability to correct metabolic (oxidative stress, non-enzymatic protein glycosylation) and immunological disorders (induction of autoimmunity, systemic inflammatory response) in diabetes. Compounds blocking these pathogenic mechanisms may be potential drugs for the treatment of this socially significant disease. Comprehensive assessment of biochemical, morphological, immunological parameters in experimental diabetes correction by 1,3,4-thiadiazine will identify their mechanisms of action, and offer optimal solutions for their application.

The project involves the search for new antidiabetic compounds among 1,3,4-thiadiazine derivatives having the properties of inhibitors of non-enzymatic protein glycosylation and antioxidants, identifying patterns of relationships in the structure, physical and chemical properties and biological activity of these compounds.

Thus, the proposed project aims to provide new approaches to prevention and drug therapy of type 1 diabetes, based on data from modern immunobiochemical, morphological studies.

Expected results:

As a result of the project a number of 1,3,4-thiadiazine compounds with antioxidant, antiglycosylating and antidiabetic effect will be selected, as well as

elucidation of the mechanisms of these types of pharmacological activity will be performed. For the first time during a three-phase experiment in silico - in vitro - in vivo complex comparative study of 1,3,4-thiadiazine derivatives will be conducted, for the prediction of their antidiabetic activity, the detection of antioxidant activity and ability to block non-enzymatic protein glycosylation as well as to correct morphological and biochemical mechanisms of regeneration of pancreatic cells and organs, which are associated with complications of type 1 diabetes (kidneys, eyes). These results may provide the basis for a new approach to the treatment of diabetes mellitus, which is based on the use of medicines that combine the properties of antioxidants, a blocker of non-enzymatic protein glycosylation and immunomodulator and will have priority in the world. According to the results of the project will be published 8 papers in journals indexed in the database Web of Science or Scopus, with the impact factor of 0.5 to 2.5 and 3 articles in journals indexed in the RSCI.

REPORTS

Annotation of the results obtained in 2016:

Understanding mechanisms of correlation between metabolic disorders and regenerative processes in pancreatic β-cells and in target organs for vascular complications in diabetes mellitus are necessary for development of new approaches to diabetes pharmacological correction. The main objective of the project is to reveal the these mechanisms and possibility of their correction with synthetic heterocyclic compound 1,3,4-tiadiazine. In order to solve the problems formulated in the Project the following experiments were performed in 2016: in silico prediction of experimental diabetes mellitus correction mechanisms with 1,3,4-tiadiazine compounds, in vitro assessment of antioxidative and antiglycating action of 1,3,4-tiadiazine compounds and in vivo assessment of immunomodulator, antioxidant and 1,3,4-tiadiazine compound effect on biochemical, hematological and morphological indices in diabetes mellitus in rats. The prediction in silico of the possible mechanisms of 1, 3, 4-tiadiazine corrective action in experimental diabetes mellitus was performed for the first time. Antidiabetic effect was predicted for 23 from 77 compounds. In addition, some compounds exhibiting multiple effects such as anti-inflammatory, immunomodulating and anti-stress were predicted. It was established on the model of the bovine serum albumin glycation that 1, 3, 4-tiadiazine compounds having morpholino or cyclo-alkylamino groups in the position 2 and phenyl or para-halogen substituted phenyl in the position 5 predominate among the compounds exhibiting the highest antiglycating activity. The antioxidative activity of 1, 3, 4-tiadiazine compounds was shown on the model of inhibiting ascorbic acid oxidation with air oxygen in vitro. A comparative analysis of the compounds was performed according to the half-maximal inhibitory concentration (IC50). The compound L-17 (2-morpholino-5-phenyl-1,3,4-tiadiazine hidrobromide) combining high antiglycating and antioxidative activity was investigated in vivo; an integrated comparative analysis of the metabolic and hematological disorders correction, morphological alteration correction in the pancreas, kidney and eye structure in alloxan diabetic rats with L-17, antioxidant lipoic acid (LA) and immunomodulator aminophtalhydrozide (APH) was performed for the first time. All tested compounds were established to correct hyperglycemia, decrease glycosylated blood proteins accumulation and modulate oxidative stress in alloxan diabetic rats. The investigated compound L-17 belonging to 1, 3, 4-tiadiazine was capable of correcting hematological and metabolic disorders in alloxan diabetes. The corrective activity of L-17 was comparable to that of antioxidant LA and immunomodulator APH. The correction of metabolic disorders with L-17, antioxidant LA and immunomodulator APH caused decrease in morphological alterations in the pancreas, kidney and eye in rats with alloxan diabetes. The application of compounds with various mechanisms of action as the correctors led to increase in the number of remaining pancreatic islets and β-cells in these islets that contributed to correction of metabolic disorders in the blood. The compound L-17 exhibiting multiple mechanisms of action decreased pancreatic islets damage but increased cellularity in a pancreatic islet. This feature of the L-17 is likely to be the especial mechanism of its antdiabetic action.

Administration of all investigated compounds in alloxan diabetes contributed to decrease in the number of damaged renal glomerulus. A significant increase in renal glomerulus size and decrease in the volume of urinary space were established when administered LA and APH in alloxan diabetes. The number of damaged glomerulus in alloxan diabetic rat kidney decreased when administered L-17, but the average area of glomerulus of the renal corpuscle was the same as in alloxan diabetic rats.

The administration of APH, LA and L-17 in alloxan diabetic rats caused the decrease in morphological alterations in the eye structure due to full or partial reparation of the vessel wall structure of microvasculature and the blood filling.

The best regenerative results obtained for eye structure, in particular for retina thickness were observed when administered APH and LA in alloxan diabetic rats.

The administration of L-17 led only to the partial reparation of morphological structure and microvasculature in the eye, but did not affect on retina thickness reparation.

Thus, at the first stage, the investigation of antidiabetic mechanisms of 1,2,3-tiadiazine action was shown to be promising. The feature of L-17 corrective action is the combination of metabolic effects (antiglycating and antioxidation) along with the correction of metabolic disorders and morphological indices in vivo (increase in pancreatic islets cellularity and partial alterations in the kidney and the retina).

A list of publications for the year as a result of the project.

1. Blinkova N.B., Danilova I.G., Gette I.F., Smirnih S.E., Pyankova Z.A., Bulavintseva T.S. The response of mast cells to liver damage in alloxan diabetes in rats //Russian Immunological Journal. 2016, №2 (1). V. 10(19). P. 543-545.

2. Emelyanov V.V., Leontyev D.V., Ishchenko A.V., Bulavintseva T.S., Cavateeva E.A., Danilova I.G. Atomic-force microscopy of erythrocytes and metabolic disorders during experimental diabetes mellitus and their correction by lipoic acid // Biophysics. 2016, V. 61 (5). P. 922-926.

3. Emelyanov V.V., Savateeva E.A., Sidorova L.P., Zeitler T.A., Gette I.F., Bulavintseva T.S., Smirnih S.E., Maximova N.E., Mochulskaya N.N., Chupahin O.N., Chereshnev V.A. 2-morpholino-5-phenyl-6H-1,3,4-thiadiazin corrects the metabolic abnormalities in the formation of alloxan diabetes in rats // Bulletin of Experimental Biology and Medicine. 2016, V. 162 (7). P.42-45.

4. Gette I.F., Danilova I.G. Effect of immunomodulator on macrophages nucleic acid content in peripheral blood lymphocytes under alloxan diabetes // Russian Immunological Journal. 2016, №2 (1). V.10 (19). P. 65-67.

5. Alexey P. Sarapultsev, Oleg N. Chupakhin, Petr A. Sarapultsev, Larisa P. Sidorova, Tatiana A. Tseitler. Pharmacologic Evaluation of Antidepressant Activity and Synthesis of 2-Morpholino-5-phenyl-6H-1,3,4-thiadiazine // Hydrobromide Pharmaceuticals. 2016, №9. P. 27.

Presentation of scientific results achieved in the scientific events (conferences, symposia, etc.).

1. Blinkova N.B., Danilova I.G., Gette I.F., Abidov M.T.1, Pozdina V.A. Features of the regenerative processes in the rat liver exposed to alloxan diabetes with stimulation of macrophages functional activity. Oral presentation. Russian conference with international participation "Experimental and computational Biomedicine" in memory of Professor Vladimir S. Markhasin, Ekaterinburg, 2016
2. Emelianov V.V., Savateeva E.A., Sidorova L.P., Tseitler T.A., Gette I.F., Bulavintseva T.S., Smirnyh S.E., Danilova I.G., Maksimova N.E., Mochulskaya N.N., Chupakhin O.N., Chereshnev V.A. 1,3,4-thiadiazine derivates – antioxidants and protein glycation blockers – for correction of experimental diabetes mellitus. Oral presentation. Russian conference with international participation "Experimental and computational Biomedicine" in memory of Professor Vladimir S. Markhasin, Ekaterinburg, 2016
3. Smirnykh S.E., Chereshneva M.V., Danilova I.G. The dynamics of the regenerative processes in the retina in rats with alloxan diabetes and after injection of tetrahydrophthalazine derivatives. Poster presentation. Russian conference with international participation "Experimental and computational Biomedicine" in memory of Professor Vladimir S. Markhasin, Ekaterinburg, 2016
4. Bulavintseva T.S., Danilova I.G. Effect of modulation of the functional activity of macrophages in the development of compensatory processes in alloxan diabetes. Oral presentation. V Annual International scientific-practical conference "Actual problems of medicine", Baku, 2016
5. Smirnykh S.E. Features of the damage of the choroid and retina in experimental diabetes and ways to correct them. Oral presentation. V Annual International scientific-practical conference "Actual problems of medicine", Baku, 2016
6. Emelyanov V.V., Ivanov A.V., Savateeva E.A., Sidorova L.P., Zeitler T.A., Gette I.F., Bulavintseva T.S., Danilova I.G., Maximova N.E., Mochulskaya N.N., Chupahin O.N., Chereshnev V.A. Poster presentation. Relationship "structure - activity" in a series of 1,3,4-thiadiazines, correcting metabolic disorders in experimental diabetes mellitus. XX Mendeleev Congress on General and Applied Chemistry, Yekaterinburg, 2016.
7. Gette I.F. Effect of immunomodulator on macrophages nucleic acid content in peripheral blood lymphocytes under alloxan diabetes. Oral presentation. I Kaliningrad Immunological Research Forum, Kaliningrad, 2016.
8. Danilova I.G. The response of mast cells to liver damage in alloxan diabetes in rats. Oral presentation. I Kaliningrad Immunological Research Forum, Kaliningrad, 2016.

Publications:

1. *Сарапульцев А.П., Чупахин О.Н., Сарапульцев П.А., Сидорова Л.П., Цейтлер Т.А.* **Pharmacologic Evaluation of Antidepressant Activity and Synthesis of 2-Morpholino-5-phenyl-6H-1,3,4-thiadiazine Hydrobromide** Pharmaceuticals, - (year - 2016).

2. *Гетте И.Ф., Данилова И.Г.* **Влияние иммуномодулятора макрофагов на содержание нуклеиновых кислот в лимфоцитах периферической крови в условиях аллоксанового диабета** РОССИЙСКИЙ ИММУНОЛОГИЧЕСКИЙ ЖУРНАЛ, - (year - 2016).

3. - **Лекарство множественного действия** газета "Уральский рабочий", 24 ноября 2016 (year -).

4. *Емельянов В.В., Леонтьев Д.В., Ищенко А.В., Булавинцева Т.С., Саватеева Е.А., Данилова И.Г.* **Атомно-силовая микроскопия эритроцитов и метаболические нарушения при экспериментальном сахарном диабете и его коррекции липоевой кислотой** Биофизика, - (year - 2016).

5. *Блинкова Н.Б., Данилова И.Г., Гетте И.Ф., Смирных С.Е., Пьянкова З.А., Булавинцева Т.С.* **Реакция тучных клеток на повреждение печени при аллоксановом диабете у крыс** РОССИЙСКИЙ ИММУНОЛОГИЧЕСКИЙ ЖУРНАЛ, - (year - 2016).

6. *Емельянов В.В., Саватеева Е.А., Сидорова Л.П., Цейтлер Т.А., Гетте И.Ф., Булавинцева Т.С., Смирных С.Е., Максимова Н.Е., Мочульская Н.Н., Чупахин О.Н., Черешнев В.А.* **2-морфолино-5-фенил-6H-1,3,4-тиадиазин корригирует метаболические нарушения при формировании аллоксанового сахарного диабета у крыс** Бюллетень экспериментальной биологии и медицины, - (year - 2016).

Annotation of the results obtained in 2017:

Using mathematical modelling in silico (calculation in IT “Microcosm”, neural simulation, quantum-chemical calculations) the search of structures in 1,3,4-thiadiazine series with co-joint antioxidant and anti-glycating activities conducted. Sample for forecast of anti-glycating activity was made based on results of anti-glycating activity study in vitro of 59 1,3,4-thiadiazines, which were tested at the first project stage. Consensus forecast of anti-glycating activity of 163 new 1,3,4-thiadiazines derivatives conducted. As a result, 13 the most promising 1,3,4-thiadiazine derivatives with potentially high anti-glycating activity were selected for future synthesis and experimental study. Using IT “Microcosm”, anti-oxidant activity level of 222 1,3,4-thiadiazines was made, 60 the most promising compounds were selected. Data bases, including 243 possible hydroxyl radical oxidate products, were assembled. 3-D models of these 243 compounds with optimization their conformation by methods of molecular mechanics and quantum-chemical modelling were built, thermodynamic parameters were calculated. Cluster allocation Gibbs free energy ΔG parameters of oxidation by hydroxyl radical of 60 promising 1,3,4-thiadiazine derivatives was made, the boundary of compounds with high anti-oxydant activity (accordingly with $\Delta G < -136,8$ kKal/moth) and 19 the most promising 1,3,4-thiadiazines with high anti-oxydant activity were detected. Consensus virtual screening of 1,3,4-thiadiazine, possess potential high anti-glycating and anti-oxydant activity detected 16 the most promising compounds for future synthesis and experimental study.

Investigation of regulatory mechanisms in the pancreatic islets at diabetes mellitus 1 (DM1) creates a base for development of promising strategies of pharmacological correction of this pathology. Hyperglycemia leads to the development of low-intensity systemic chronic inflammation and forms chronic complication of the DM1, such as microangiopathy, nephropathy and retinopathy. It is known, that inflammatory and autoimmune reactions,

controlled after immunocompetent cells in blood and tissue and cytokine-mediated, take place at DM1. Regulation of inflammatory reaction at DM by immunocompetent cells is carried out through secretion of such proinflammatory cytokine, as interferon gamma (IFN-γ), interleukin 1 (IL-1) and interleukin 1 (IL-1). Intensive pharmacology screening is focused on chemical compounds with pleiotropic action, combined ability to correct metabolic (oxidative stress, non-enzymatic glycosylation of proteins) and immunological disorders (induction of autoimmune reaction, systemic inflammatory response). Compounds, blocking these pathogenic mechanisms, may become potential drugs for therapy this socially significant disease.
The main goal of the project in 2017 was clarification of the possibility of using synthetic heterocyclic 1,3,4-thiadiazine compounds to correct system inflammatory response, morphological and biochemical disorders under conditions of experimental alloxan diabetes mellitus. To achieve these goals a set of studies was carried out at three levels: in silico (directed search of derivatives of 1,3,4-thiadiazine with combined antioxidant and anti-glycating activities, in vitro (investigation of anti-glycating action of 1,3,4-thiadiazine compounds, differing by nature of substituent in position 2 and 5 of heterocycle at composition with ascorbic acid) and in vivo (effect of 1,3,4-thiadiazine, differing by nature of substituent in position 2 and 5 of heterocycle and their composition with ascorbic acid at morphological, biochemical, immunological and hematological values at rats in the model of alloxan diabetes mellitus).

Take into consideration the early established ability of 1,3,4-thiadiazine to transform into thiol derivatives, which perform synergism with ascorbic acid in the antioxidant system, it is interesting to compare results of the correction of alloxan DM by 1,3,4-thiadiazine and their pharmaceutical composition with ascorbic acid. The possibility to increase anti-glycating action of 1,3,4-thiadiazines by combination them with ascorbic acid was investigated in the model system in vitro. It was established, that reinforcement of anti-glycating action is not general and is observed only for 2-pyrrolidine-5-[2,5-dichlorothienyl]-1,3,4-thiadiazine and 2-piperidino-5-[2,5- dichlorothienyl]-1,3,4-thiadiazine.
At the experiment first was established, that administration of 2-morpholino-5-phenil-1,3,4-thiadiazine (L-17 compound), its composition with ascorbic acid and compounds of comparison (lipoic acid, ascorbic acid, immune modulator aminophtalgydrazid (AFG) leads to the decrease of IFN-γ, IL-1α and IL-10 levels in alloxan DM at rats. L-17 compound possess the greatest action. Composition of L-17 compound with ascorbic acid doesn't increase its action.
Was discovered the macrophage infiltration of pancreas under the alloxan DM. After the administration of L-17 compound, its composition with ascorbic acid and lipoic acid, the macrophage number decrease only in the exocrine tissue of pancreas. The assessment of immune phenotype of pancreas-infiltrating macrophages discovered decrease of the quantity of M2 macrophages.
Administration of compounds 1,3,4-thiadiazine series, differing by nature of substituent in position 2 and 5 of heterocycle and their composition with ascorbic acid adjusted biochemical values and functional activity of β-cells in the Langerhans islets. The ability of test compounds to reduce hyperglycemia, to decrease accumulation of glycosylated hemoglobin and fructosamine, to correct the oxidative stress state and to prevent insulin concentration decline in blood plasma under the alloxan DM established. It confirms by morphological and morphometrical investigation, according to which L-14 compound (2-propilmorpholino-5-phenil-1,3,4-thiadiazine) prevents islets destruction and decrease of β-cells number in them. Simultaneous administration of ascorbic acid with L-17 compound amplify its regenerative action on islets, with L-14 compound – reduce it. Positive influence of test compounds on hematological indices, which is manifested by increasing of red blood cells, hemoglobin and hematocrit at rats under experimental diabetes.
Therefore, the conducted research first showed the possibility of simultaneous correction each of hyperglycemia, hypoinsulinemia, glycation of proteins, oxidative stress systemic inflammatory response and pancreatic islets structure parameters, using 1,3,4-thiadiazines and their pharmaceutical combination with ascorbic acid.
Oxidative stress, protein glycosylation and systemic inflammatory response are general diabetes characteristics and they take place not only in DM1, but also in DM2. Concerning it, DM2 model (intraperitoneal injection of streptozotocin and nicotinamide [Spasov A.A. and others] was tested. In the future it will allow to estimate the effect of tested in the project's boundaries compounds during the modelling of DM2.
Take into account proven pleiotropic action of 1,3,4-thiadiazines, these compounds are high promising for future profound study of possibility to use them in DM.

A list of publications for the year as a result of the project:

Danilova I.G., Emelyanov V.V., Gette I.F., Medvedeva S.Y., Bulavintseva T.S., Chereshneva M.V., Sidorova L.P., Chereshnev V.A. , Sokolova K.V. Cytokine regulation of regenerative processes in pancreas in alloxan diabetes mellitus in rats and its correction by compound of 1,3,4-thyadiasine series and lipoic acid // Medical Immunology. – 2018.

Emelyanov V.V., Shmakova S.E., Chereshnev V.A. Immuno-endocrine interactions in alloxan diabetes mellitus in rats and its correction by lipoic acid // Russian Journal of Immunology. – 2017. - Vol. 11-20. - № 2. – P. 372 – 374.

Emelyanov V.V., Ivanov A.V., Sidorova L.P., Tseitler T.A., Gette I.F., Bulavintceva T.S., Danilova I.G., Maksimova N.E., Mochulskaya N.N., Chupachin O.N., Chereshnev V.A. Relationship "structure-activity" in a series of 1,3,4-thiadiazines, correcting metabolic disorders in experimental diabetes mellitus // Izvestiya AN. Ser. Khim. – 2017. - № 10. – P. 1873 – 1875.

Bulavintcena T.S., Danilova I.G. Macrophages responsibility in the local regulation of pancreas islet apparatus in alloxan diabetes // Medical Immunology. - 2017. – Volume 19. – P. 18.

Irina G. Danilova, Tatyana S. Bulavintceva, Irina F. Gette, Svetlana Yu. Medvedeva, Victor V. Emelyanov, Musa T. Abidov Partial recovery from alloxan-induced diabetes by sodium phthalhydrazide in rats // Biomedicine & Pharmacotherapy. -2017. - № 95. – P. 103 – 110.

Blinkova N.B., Danilova I.G., Abidov M.T. Macrophage modulation as a factor of regeneratory processes' regulation in liver in alloxan diabetes in rats // Cells and Genes. - 2017. – Vol. XII. - № 3. – P. 44.

Blinkova N.B., Danilova I.G., Gette I.F., Bulavintceva T.S. Response of immunocompetent cells for structural renal disorders in experimental alloxan diabetes // Russian Journal of Immunology. - 2017. – Vol. 11 (20). - № 2. – P. 257 – 258.

Emelyanov V.V., Bulavintceva T.S., Sidorova L.P., Tseitler T.A., Chupachin O.N., Cherechnev V.A. Level of cytokinemia in alloxan diabetes mellitus and its correction by compound of 1,3,4-thiadiazine series // Medical Immunology. - 2017. - Vol. 19 – P.28.

Publications:

1. *Емельянов В.В., Булавинцева Т.С., Сидорова Л.П., Цейтлер Т.А., Чупахин О.Н., Черешнев В.А.* **Уровень цитокинемии при аллоксановом сахарном диабете у крыс и его коррекция соединением ряда 1,3,4 – тиадиазина** Медицинская иммунология, Том 19. - С.28. (year - 2017).

2. *Данилова И.Г., Булавинцева Т.С., Гетте И.Ф., Медведева С.Ю., Емельянов В.В., Абидов М.Т.* **Partial recovery from alloxan-induced diabetes by sodium phthalhydrazide in rats** Biomedicine & Pharmacotherapy, # 95.- P. 103–110 (year - 2017).

3. *Блинкова Н.Б., Данилова И.Г., Абидов М.Т.* **Модуляция макрофага как фактор регуляции регенераторных процессов в печени крыс с аллоксановым диабетом** Клетки и Гены, Том XII. - № 3. - С. 44. (year - 2017).

4. *Булавинцева Т.С., Данилова И.Г.* **Роль макрофагов в локальной регенерации островкового аппарата поджелудочной железы при аллоксановом диабете** Медицинская Иммунология, Том 19. - С. 18. (year - 2017).

5. *Данилова И.Г., Емельянов В.В., Гетте И.Ф., Медведева С.Ю., Булавинцева Т.С., Черешнева М.В., Сидорова Л.П., Черешнев В.А., Соколова К.В.* **Цитокиновая регуляция регенеративных процессов в поджелудочной железе при аллоксановом сахарном диабете у крыс и его коррекция соединением ряда 1,3,4-тиадиазина и липоевой кислотой** Журнал «Медицинская иммунология»., - (year - 2018).

6. *Блинкова Н. Б., Данилова И. Г., Гетте И. Ф., Булавинцева Т. С.* **Реакция иммунокомпетентных клеток на структурные повреждения почки при экспериментальном аллоксановом диабете** Российский иммунологический журнал, Т. 11 (20). - № 2. - С. 257 - 258. (year - 2017).

7. *Емельянов В. В., Шмакова С. Е., Черешнев В. А.* **Иммуно-эндокринные взаимодействия при аллоксановом сахарном диабете у крыс и его коррекции липоевой кислотой** Российский иммунологический журнал, Т. 11(20). - № 2. - С. 372 - 374. (year - 2017).

8. *Емельянов В.В., Сидорова Л. П., Саватеева Е.А., Булавинцева Т.С., Гетте И. Ф., Максимова Н.Е., Мочульская Н.Н., Черешнев В.А., Чупахин О.Н.* **Применение фармацевтической композиции 2-морфолино-5-фенил-6Н-1,3,4-тиадиазина с аскорбиновой кислотой в качестве средства коррекции аллоксанового сахарного диабета** -, 2626677 (year -).

9. *Емельянов В.В., Иванов А.В., Саватеева Е.А., Сидорова Л.П., Цейтлер Т.А., Гетте И.Ф., Булавинцева Т.С., Данилова И.Г., Максимова Н.Е., Мочульская Н.Н., Чупахин О.Н., Черешнев В.А.* **Взаимосвязь структура—активность в ряду 1,3,4-6Н-тиадиазинов, корригирующих метаболические нарушения при экспериментальном сахарном диабете** Известия Академии наук. Серия химическая, № 10. - С. 1873 - 1875. (year - 2017).