

G.G. Meyramov<sup>1</sup>, V.I. Korchin<sup>2</sup>, A.S. Shaybek<sup>1</sup>, A.P. Andreewa<sup>3</sup>,  
G.O. Zhuzbaeva<sup>1</sup>, D.A. Meyramova<sup>1</sup>, A.G. Abdraimova-Meyramova<sup>4</sup>

<sup>1</sup>*Ye.A. Buketov Karaganda State University, Kazakhstan;*

<sup>2</sup>*Medical Academy, Hanty-Mansyisk, Russia;*

<sup>3</sup>*Immanuel Kant Baltic Federal University, Kaliningrad, Russia;*

<sup>4</sup>*Medical University of Karaganda, Kazakhstan*

*(E-mail: meyradow@mail.ru)*

## On the chemical mechanisms of interaction of diabetogenic toxic substances with zinc in the pancreas and methods for its prevention

Article presents data on chemical mechanisms of binding of Zinc in pancreas of animals and human by diabetogenic chelate active chemicals (DZC) that result destruction and death of pancreatic B-cells within a few minutes and of developing of diabetes mellitus. Authors presented and described a few mechanisms for prevention of binding of Zinc in pancreas that result prevention developing of experimental diabetes in 95–100 % of animals. The authors analyze and substantiate in details on the basis of own investigations (1964–2018), the chemical mechanisms of zinc blocking in cells, which prevents the possibility of their destruction caused by diabetogenic zinc-binding substances, the possibilities of human contact with which have significantly increased over the past decades. According to the results of our own studies and literature data, the chemical mechanisms of the preventive action of derivatives of Dithiocarbamic acid, amino acids — reduced glutathione, cysteine and histidine, as well as the possibility of chemical neutralization of the blood of the DCS before they reach the pancreas, were investigated.

*Keywords:* zinc, B-cells, Diabetogenic zinc binding chemicals, Glutathione, Diphenylthiocarbazon (Dithizon).

*Abbreviations:* DZC — Diabetogenic zinc binding chemicals; DZ — Diphenylthiocarbazon (Dithizon); GRF — Glutathione restored form; GOF — Glutathione oxidised form; NaDDCA — Na salt of Diethyldithiocarbamic acid; 8TSQ — 8-para(toluenesulphonylaminoquinolin).

### Introduction

More than 80 years ago Scott and Fischer were separated insulin from the native pancreas as Insulin-Zn complex and supposed that the presence of Zn-ions determined physiological activity of insulin [1, 2]. Interest for this problem is increased after reporting that in pancreas of diabetic patients total amount of Zn is not more than 50 % in compared with non diabetic men. They found 0.07 mg of Zn per 1g of pancreas tissue of diabetic patients comparatively with 0.14 mg per 1g pancreas of healthy persons. Analogical result was obtained by Eisenbrandt and coll. [3]. A large amount of Zn<sup>+2</sup>-ions was found in human pancreas of healthy men. Okamoto K. discovered in pancreatic B-cells a large amount of Zn<sup>+2</sup> [4]. It is supposed today the important role of Zn-ions in processes of storage of insulin in B-cells [5, 6]. There are proportional dependence between content of Zn-ions in B-cells and in cytoplasm. Decreasing of content of deposited insulin accompanied by decreasing of amount of Zn-ions in B-cells. It is known that Zn-ions take part in processes of synthesis as in crystallization of insulin. It was showed that pancreas of mammals-animals, human, birds and in earth-water animals contained a large amount of Zn-ions.

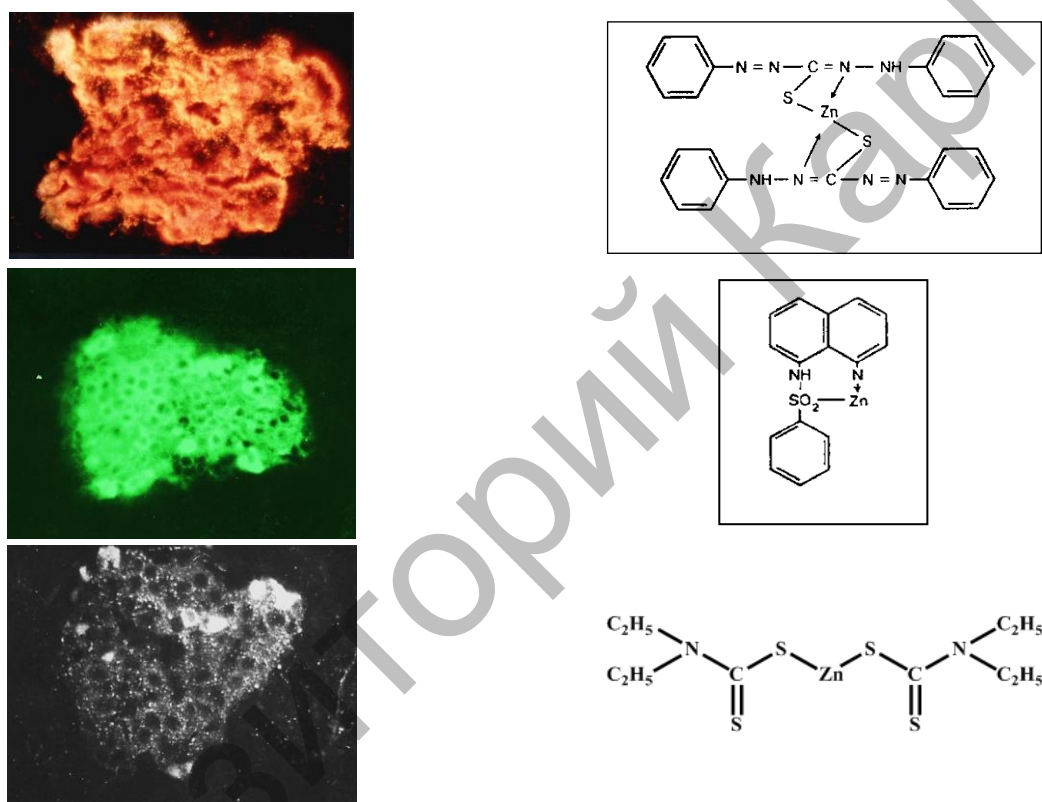
Today, more than 20 chemicals are known that can selectively damage B cells in the body, which leads to their rapid death. Of these, 18 substances belong to the group of diabetic zinc-binding substances that form in complex B cells intracellular salts (chelates) with zinc contained in B cells, which leads to their rapid death. The authors investigated the chemical mechanisms of the formation of zinc-chelator complexes [7]. It was shown which parts of the DCS molecules and through which atoms they form chelates with zinc. Based on the studies, it was shown that the preventive effect of zinc blocking by non-diabetogenic substances is realized through interaction with the sulfur and nitrogen atoms of the DZC, that is, through the same atoms with which the DCS form complexes toxic to cells. Regarding the preventive action of the amino acids glutathione and cysteine, it was shown that their preventive effect is due to the blocking of the zinc atom through the sulfur atoms of SH radicals, which prevents the interaction of zinc with DZC. The Zn-ions in cytoplasm of B-cells have the coordinate number 4 and 6 and interacted with chemicals which formed with Zn-ions chelat salts in

which atom of  $Zn^{+2}$  is fixed between a few other atoms [8]. The affinity of Zn-ions to formation of chelates is evidently more high comparatively with other metals of main group.

### Diabetogenic activity of Zinc-binding chelators Dithizon and derivatives of 8-oxyquinoline

From the more than 20 chemicals that cause selective destruction of B-cells, 18 are represented by derivatives of 8-hydroxyquinoline and Dithizon (Diphenylthiocarbazon) (Fig.1).

Dithizon (diphenylthiocarbazon) is one of most active chelators [4, 9]. Dithizon formed various modifications of red colour chelates with 18 metals. It possesses a marked high affinity to Zn-ions and formed very rapidly past injection chelate 2:1 that accompanied by destruction and death of B-cells within 15–30 min. and developing of 1<sup>st</sup> type of diabetes 24–48 h later. It was showed that first changes in cytoplasm of B-cells appeared 5 min past injection of DZ as small zones of destruction of cytoplasm. More detail analysis using of transmission electron microscopy showed that process of destruction of B-cells started by destruction of B-granules.



From above: 1) red granules; chelat complex Zinc-Dithizon in B-cells and disposition of atom of Zinc in complex; result destruction and death of B-cells; 2) green fluorescence of chelat complex Zinc-8PTSQ in B-cells and disposition of atom of Zinc in complex; result destruction and death of B-cells; 3) white granules: chelat complex Zinc-NaDDCA; protect B-cells of destruction

Figure 1. Various chelat complexes Zinc-chelator

For the first, the 2–3 B-granules are destructed with forming of small zones of destruction of cytoplasm of B-cells [10], not more than 3–5 % of total surface of section of B-cells. 15 min later the sizes of these zones rapidly increased until 30–40 % of surface of B-cells and 1–2 h past injection almost all cell's matrix, 80–90 % of section's surface, is destroyed completely. It is showed that these changes are not visible on light microscopy but very well discovered by transmission electron microscopy. Destructive histological changes developed a few days later — are secondary changes as result of not visible destroying of B-cells within first few minutes after forming of chelate complex in cytoplasm of B-cells. Thus, it was concluded that destruction of B-cells past injection of diabetogenic doses of Dithizon and of 8TSQ is determined by action of complex Zn-DZ and Zn-8TSQ on structure, for the first, on B-granules of B-cells, where is concentrated zinc as deposited form “zinc-insulin complex” within first 15–30 min. past forming of complex in cytoplasm of B-cells (Fig. 1).

### Diabetogenic derivatives of 8-oxyquinoline

A. Albert in 1947 reported that 8-oxyquinoline which usually belong to not toxic substances, is very toxic for cells in the presence of metals and for the first time — of Zn-ions. It was showed that this fact determined by ability of 8-oxyquinoline to form with metals the chelate metal-complexes which are toxic for B-cells [11, 12] as complexes formed in B-cells by other chelate active substance as Dithizon. Studying of toxicity of 8-oxyquinoline for B-cells K. Okamoto [9] reported that injection of it to animals accompanied by developing of experimental diabetes. Later it was showed that injection of 18 derivatives of 8-oxyquinoline and of 8-oxyquinaldin accompanied by rapid developing of heavy diabetes in animals. It was noted that all these chemicals have in position 8 of quinoline ring OH-group or any other radical contained atom of S or atom of O. Six isomers of 8-oxyquinoline not contained in position 8 of the active group are not able to form chelate complexes with Zn-ions and not induced experimental diabetes. Experimental diabetes is induced by derivatives as 8-para(toluenesulphonylamino)quinoline /8PTSQ/, 8-para(benzenesulphonylamino)quinoline /8PBSQ/, 8-para(methansulphonylamino)quinoline /8PMSQ/, 5-para(acetaminophenylazo)-8-oxyquinoline /5A8OX/, 8-hydroxyquinaldin, 5-amino-8-hydroxyquinoline and others (Fig. 2, 3). It was demonstrated [9] that injection of these derivatives result selective necrosis of B-cells and developing of diabetes. Injection of these chemicals in doses of 30–100 mg/kg accompanied by developing within a few days of heavy diabetes with marked degenerative changes in islets.

### On the chemical mechanisms of binding of Zinc-ions by derivatives of 8-oxyquinoline

It is known that most stable complexes are formed when atom of Zn is fixed between 2 atom of N, S and O of molecule of chelator. Later it was reported that only derivatives of 8-oxyquinoline contained in position 8 of quinoline ring of the hydroxyl or other radical contained atoms of S, N or O possess diabetogenic properties. Atom of Zn is fixed between atoms of O in position 8 and of N in position 1 or between two atoms of O in positions 2 and 8 (xanthurenic acid) (Fig. 3).

It was reported, what is more, that extraction of these radicals from position 8 accompanied by complete disappearing of diabetogenic properties of chelators [9]. Formation of chelats by atoms of O and N of chelator result usually forming of pentagonal or hexagonal rings [8, 9] (Fig.3). Pentagonal rings are more stable. The most stable are quadrangular complexes with atom of S. Electrons of indivisible pair are displaced from donor atom of N in position 1 to Zn atom.

On the base of data obtained by A. Albert, it was supposed that toxic effect of 8-oxyquinoline is determined by its ability to bind and eliminate ions of metal from B-cells. But later this hypothesis was not confirmed: it was showed that long time prolonged elimination of Zn-ions from B-cells result any effect on the state of histostructure and function of B-cells [10].

Finally, S. Rubbo and A. Albert established that toxic effect of 8-oxyquinoline determined by its ability to form in cells toxic complexes with metals [11] that many times was confirmed later. It was showed that presence of chelate a short time in cytoplasm of B-cells accompanied by alteration of cells. In experiences with using derivatives of 8-oxyquinoline — a various isomers of the azaoxyquinoline (azaoxyn) — it was demonstrated dependence: most toxic are isomers formed chelats 1:1 with metal have logarithm of constant of stability as 7.6 and more high, until 9.4. Meanwhile toxicity of chelats of other isomers of azaoxyn with constant of stability 5.8–6.7 were clearly more less [12]. It was showed that very toxic chelats of derivatives of 8-oxyquinoline with Zn-ions have a more high logarithm of constant of stability as 8.5. Weitzel G. and coll. showed that complex 1:1 contained 1 molecule of 8-oxyquinoline and 1 atom of ion of Zn is most toxic for cells [13].

Stability of formed complexes 2:1, as complex Dithizon-Zinc, is depended not only of affinity of chelator to metal but in added — by 2 properties of chelator and metal: 1) presence of additional radicals in parapositions molecule of chelator, especially — in zones which contacted with part of molecule, reacted with ions of metal conduce to forming of the steric effect; as result, two molecules of chelator are not able to approach for to put atom of metal in stable ring; 2) size of diameter of atom; in case if atom of metal have a small diameter, ring may be not formed; atom of Zn have radius as 0.74 nm between Berillium (0.31 nm) and Rubidium (1.49 nm). A high stability of complex Zn-Dithizon is determined by stretch form of molecule of Dithizon and by location of 2 phenol rings on the 2 ends of molecule. That is why atom of N and S are easy approach to atom of Zn. More over, atom of Zn is fixed between atoms of N and S. Meanwhile it is known that affinity of Zn to N and S is more high comparatively with affinity of Zn to O. In added, complex is formed by two molecule of Dithizon each of two have a great number of double couplings (Fig. 3).

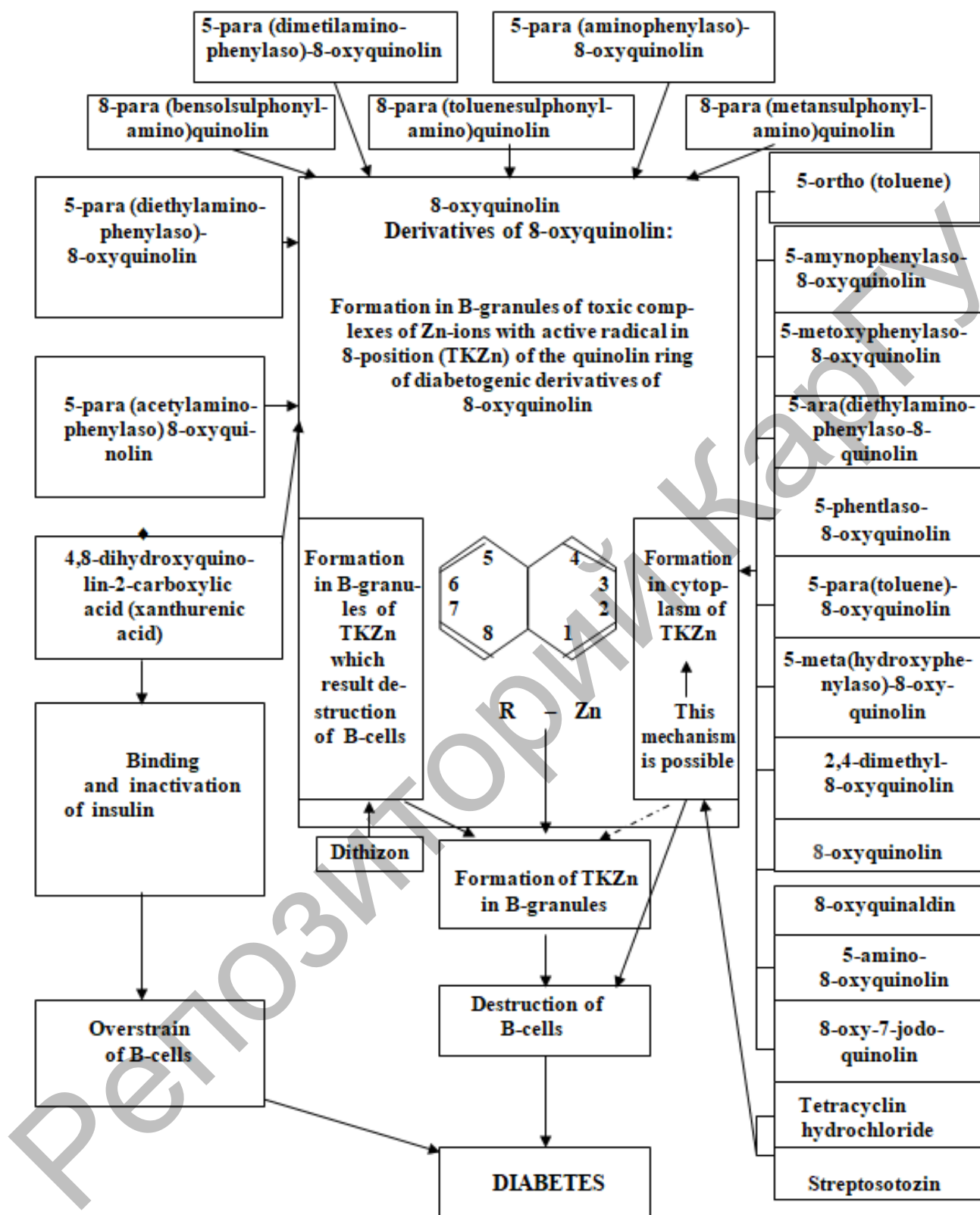
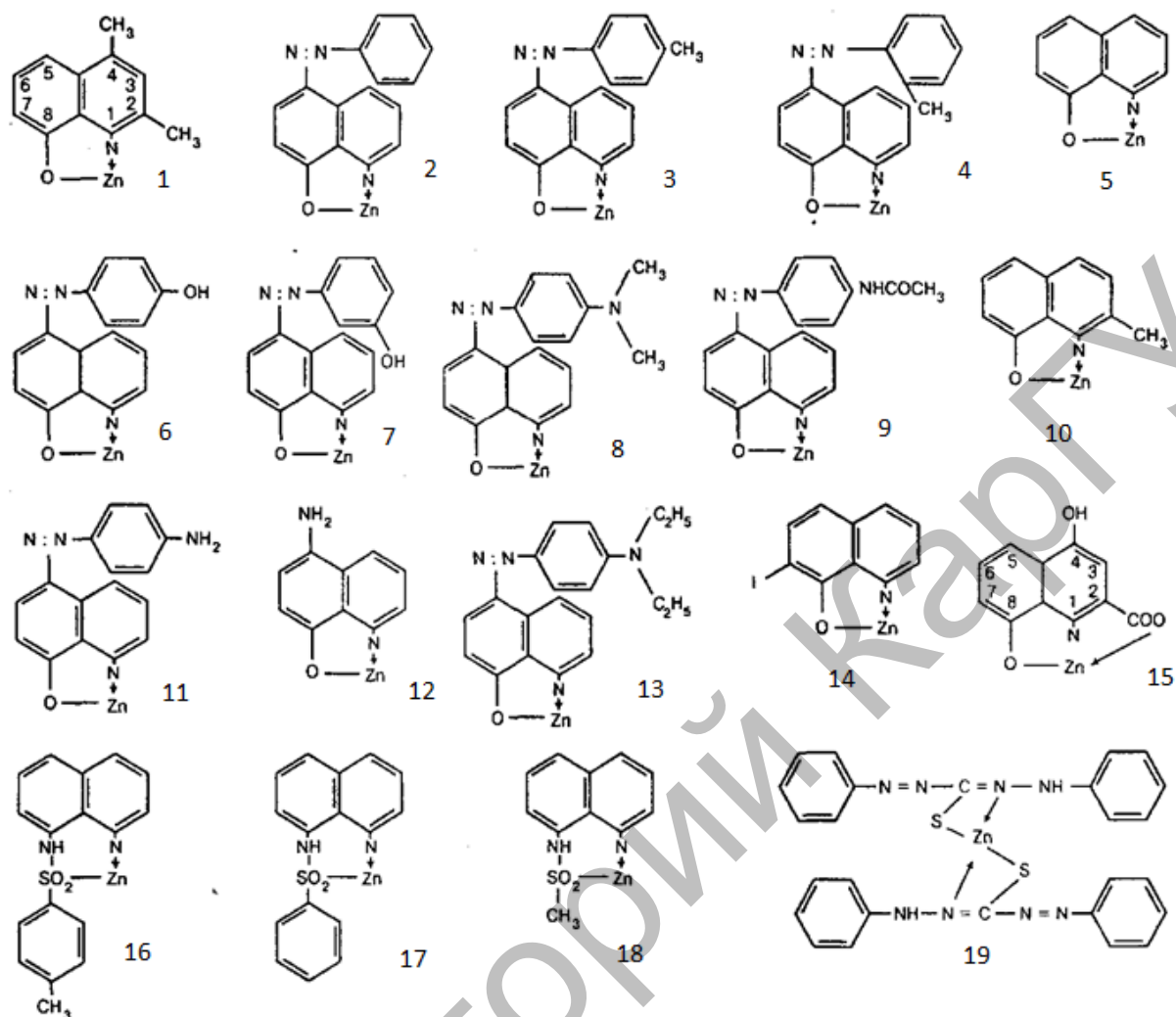


Figure 2. Mechanisms of damage of B-cells caused by diabetogenic chelat active chemicals (♦ — synthesized in human) (by Meyramova A.G. and Meyramov G.G., 2016)

Stability of complexes 1:1 formed by derivatives of 8-oxyquinoline is determined by a: 1) great number of double coupling in molecule of chelator; 2) forming of quadragonal ring; 3) derivatives of 8-arensulphonyl-aminoquinoline formed chelat-complex by aid of atom of S. Stability of the complex Zn-Xanthurenic acid is determined in added by fixation of the atom of Zn between 2 atom of O [9] (Fig. 3).



- Compounds: 1 — 2,4-dimethyl-8-oxyquinoline, 35 mg/kg; 2 — 5-phenylazo-8-oxyquinolin, 20 mg/kg; 3 — 5-para(toluene)-8-oxyquinoline, 20 mg/kg; 4 — 5-orto(toluene)-8-oxyquinoline, 40 mg/kg; 5 — 8-oxyquinoline, 50–60 mg/kg; 6 — 5-para(diethylaminophenylazo)-8-oxyquinoline, 20 mg/kg; 7 — 5-meta(hydroxyphenylazo)-8-oxyquinoline, 30 mg/kg; 8 — 5-para(dimethylaminophenylazo)-8-oxyquinoline, 45 mg/kg; 9 — 5-para(acetylamino phenylazo)-8-oxyquinoline, 50 mg/kg; 10 — 8-oxyquinaldin, 10 mg/kg; 11 — 5-para(aminophenylazo)-8-oxyquinoline, 10 mg/kg; 12 — 5-amino-8-oxyquinoline, 30 mg/kg; 13 — 5-para(diethylaminophenylazo)-8-oxyquinoline, 40 mg/kg; 14 — 9-oxy-7-jodoquinoline, 50–60 mg/kg; 15 — 4,8-dihydroxyquinolin-2-carboxylic acid (xanthurenic acid); 16 — 8-para(toluenesulphonylamino)quinoline, 30–50 mg/kg; 17 — 8-(benzenesulphonylamino)quinoline, 30–100 mg/kg; 18 — 8-(metansulphonylamino)quinolin, 40–81 mg/kg; 19 — diphenylthiocarbazonate (Dithizon), 45–50 mg/kg

Figure 3. Complex salts of Diabetogenic zinc-binding chelate active chemicals with Zn-ions and its Diabetogenic doses (by Meyramova A.G., 2003)

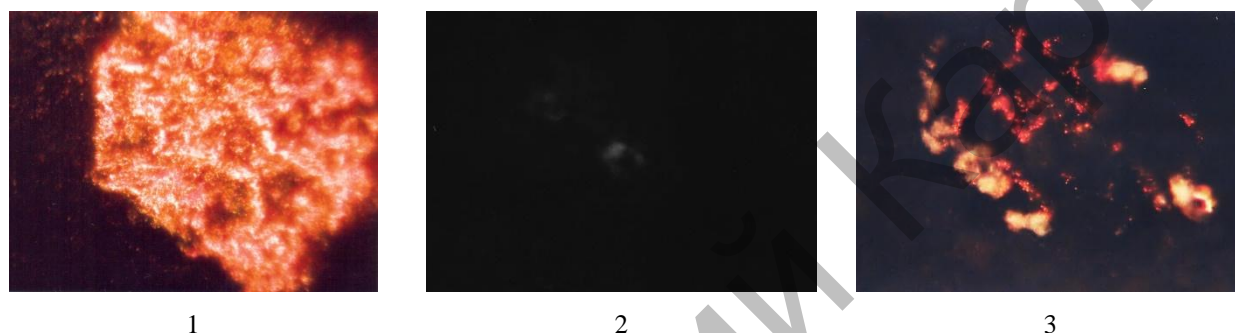
Using of transmission electron microscopy method it was established that 2h past injection of Dithizon a strongly marked destruction of B-cells was developed: total devastation of cytoplasm of cell's matrix; destruction of mitochondria, endoplasmic reticulum and B-granules were discovered in the most parts of cells with remained matrix [7, 12]. Same results were obtained 1h later injection. Shortening of period since starting of injection showed that 15 min past injection in the contrary to 2h cell's matrix was remained on 80–90 % of B-cell's surface but 30–40 % appeared as zone free of matrix or zone of complete destruction of ultrastructures of B-cells [10]. Mechanisms of diabetogenic action of DZC are presented at Figure 2.



### Chemical mechanisms of the methods for prevention developing of diabetes caused by chelators. Mechanisms of protective effect of aminoacids Glutathione and Cystein

The aminoacids Glutathione and Cystein formed not toxic chelates with atoms of heavy metals due to sulfhydryl radicals which have high affinity to ions of  $Zn^{+2}$ ,  $Pb^{+2}$ ,  $Cd^{+2}$  and  $Hg^{+2}$ . It is suggested that by these radicals aminoacids formed not toxic chelates with Zn-ions. The constant of stability of complex Zn-Glutathione is very high — 17.1–18.2.

Diabetes caused by DZC is prevented by Restored form of Glutathione (GRF). Preventive injection GRF, 1000 mg/kg protect B-cells of rabbit's pancreas of binding of Zinc ions by DZ (Fig. 4) and from destruction and of developing of diabetes in all animals: normoglycemia and B-cells — without changes [14]. Meanwhile, oxydation of GRF result: two molecules of GRF formed one molecule with formation of disulfide connection (Fig. 5). Thus, oxidized form of glutathione (GOF) have same structure but contrary to GRF not contain in structure of molecule of SH-radical not protect B-cells of formation of complex Zn-DZ that result destruction of cells. Injection to animals of 1000 mg/kg of GOF not protect B-cells of destruction by DZC and diabetes developed in all animals [15, 16].



1 — Negative fluorescent reaction for Zinc in B-cells (absence of fluorescence) as result of binding of Zinc with GRF; high specific for Zinc reaction with 8PTSQ;  $\times 140$ ; 2 — Injection of GRF and 3 — 10 min later of DZ; prevention of formation of complex Zn-DZ as result of blocking of Zinc by GRF; darc microscopy;  $\times 280$

Figure 4. Red granules of complex Zn-DZ in B-cells of rabbit; staining by DZ; darc microscopy;  $\times 280$

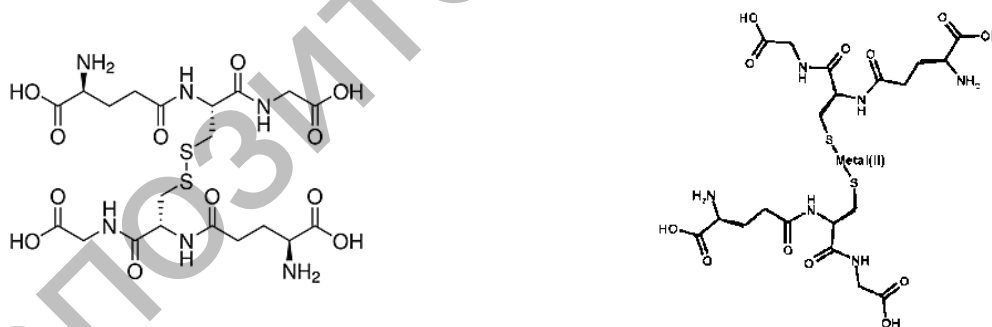


Figure 5. Disposition of Zinc atom between 2 atoms of S of two SH-groups from 2 molecules of GRF (by F.M. Rubino. Toxicity of Glutathione-Binding Metals: A Review of Targets and Mechanisms. Toxics, 2015, 3(1), 20–62)

The GRF easily reacts with free radicals among which it should be noted hydroxylic and carbon radicals, giving Hydrogenium atom. Similar interactions provide protection, neutralizing the fissile  $OH^{\cdot}$  radical which is considered as the most dangerous among the free radicals. Decrease of amount of GRF increases susceptibility of animals to cytotoxins [17]. SH-radical possess chemical resistance against influence of peptidases.

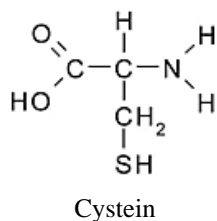
Its polygonality determined by chemical properties and allows to be simultaneous both the nucleophilic agent and the fissile reducer, interacting with numerous elektrofilny and oxidizing components, such as  $N_2O_2$ ,  $O_2$  and  $OH^{\cdot}$ . GRF as active reducer plays an important role in processes of a detoxification.

Glutathione is used for prevention and treatment of diabetic neuropathy in the streptozotocin-induced diabetic rat [18]. It was supposed that inactivation or change of SH-group of sulfhydryl radicals in molecules

of Glutathione result complete disappearing of protective properties of the formed in result of Oxidized form of Glutathione.

It is evidently easy and clear to suppose that preventive effect Restored form of Glutathione is determined by inactivation of SH-radicals of two molecules of GRF and fixation of atom of Zinc between two atoms of S to which Zinc possess a high affinity (Fig. 5).

Injection of Cystein, 1000 mg/kg prevent formation in B-cells of toxicchelate Zn-DZ an complete prevention of diabetes in all animals within 6 h; 12 h past injection diabetes was prevented in 6 animals from 8 and 24 h past injection of Cystein — in 2 animals from 4. Cystein protect B-cells of destruction caused by diabetogenic derivatives of 8-oxyquinoline [19]. Aminoacid Serin, which contains hydroxyl radical in molecule instead of sulfhydryl radical in molecule of Cystein, not possess diabetogenic properties.



Aminoacid Hystidine formed with Zn-ions high stable complex 2:1 which logarithm of constant of stability is 12.0. Contrary to other aminoacids chelate activity of Hystidin is determined by the presence in molecule of the imidazol ring [8]. Injection to animals 1000 mg/kg of the Hystidin Hydrochloride (HH) result complete prevention of diabetes past injection of Dithizon followed 5 min past injection of HH and — in half of total number of animals injected of Dithizon 0.5–1 h past injection of HH [20].

#### Chemical mechanisms of protective effect of derivatives of Dithiocarbamic acid

Derivatives of Diethyldithiocarbamic acid (DDC) possess a high affinity for Zinc ions as EDTA were conducted. Na salt of DDC is able not only to prevent developing of diabetes caused by DZ but to displace of DZ from formed in B-cells complexes as Zinc-DZ due to more high affinity to Zinc. EDTA as chelator possess more high affinity to Zn and constant of stability of its chelats with Zn is 13.1 meanwhile with ions of  $Mg^{+2}$ ,  $Ca^{+2}$  and  $Fe^{+3}$  correspondly 5.4, 7.3, and 10.9 (10). It was showed that EDTA prevent diabetogenic action of streptozotocin by binding of Zn-ions. More detail investigation of processes of interaction of Zn-ions contained in B-cells with NaDDC showed that injection of 1000 mg/kg to rabbits result complete binding of all amount of Zn-ions in B-cells that accompanied by formation in B-cells of not toxic chelate complexes 2:1 as Zinc-NaDDC (10) (Fig. 6). Atom of Zinc is fixed between of two atoms of S from the two molecules of NaDDC. Followed injection of DZ not accompanied by formation of toxic Zn-DZ complex in cytoplasm of B-cells and diabetes not developed. Thus, finally it was confirmed that presence of toxicchelate complexes of DZ and diabetogenic derivatives of 8-oxyquinoline in B-cells within first 15–30 min after its forming result not visible for the first a few hours incorrigible destructive changes in B-cells. Formed more later degenerative histological changes in islets is result of action of chelators in the first 15 min.

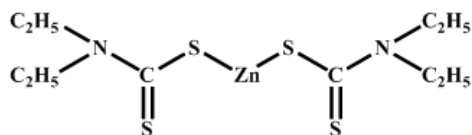


Figure 6. Fixation of atom of Zinc between two atoms of S of the two molecules of NaDDC

It is known that Streptozotocin possess chelate properties and have high affinity to Zn-ions. Alternative action of Streptozotocin may be prevented or eased by preventive action of EDTA [21].

Investigation of diabetogenic properties of Dithizon and derivatives of 8-oxyquinoline have theoretical significance because these chemicals are not formed in human and really. In added peroral administration of its is not effective because they are not soluble and not absorbed in intestinum. Parenteral injection of diabetogenicchelators result developing of diabetes only. Solutions of all these chelators are not stable and only injection of the fresh prepared solutions (ex tempore) result diabetogenic effect. Meanwhile some antimicrobial drugs widely used for treatment of skin diseases contains derivatives of 8-oxyquinolin as main antimicrobial component.

Among 18 diabetogenic derivatives of 8-oxyquinoline the Xanturenic acid (XA) only is formed in animals and elderly humans in deficiency of Pyridoxine. It is known that XA is accumulated in organism of old human as result of disturbances of Tryptophan metabolism. Low doses of the XA accumulated in human gradually. May be that is why diabetes caused by XA developed gradually as type 2 in opposite to type 1 diabetes caused by injection of diabetogenic doses of other chelators. High concentration of XA in the urine decrease by long time prolonged using of Pyridoxine [22] that accompanied by decreasing of blood glucose concentration as weakening of symptoms of diabetes.

The number of diabetogenic chelators human have contacts is increased year by year. As example Tetracycline hydrochloride is active chelator which have high affinity to Zn-ions and formed with it complex 1:1 and 2:1 with high constant of stability as 9.0 [11]. Direct action on B-cells of high doses of tetracycline result hyperplasia and degeneration of cells. Isoniazid, a drug for treatment of tuberculosis, formed pentagonal stable chelats with Zn-ions. May be more high frequency of diabetes among patients treated by Isoniazid determined by this fact? This interest is increased taking into consideration fact that in this case concentration of the Xanturenic acid in urine is high because Isoniazid in antagonist of Pyridoxal-5-Phosphate.

Dehydroascorbic Acid (DA) which is formed me symptoms of diabetes on animals as of soluucose level id in organism as result of metabolisation of Ascorbic Acid, possess diabetogenic properties and result direct alterative effect on B-cells. Concentration of DA in organism of diabetics is evidently increased in opposite to decreasing concentration of Ascorbic acid.

It is known that chelators which formed with Zn-ions tetragonal or pentagonal rings possess diabetogenic properties. Chelators contains in molecule as least 4 or 5 double chemical connections possess diabetogenic properties also in opposite tochelators contained 1–2 or not contained its which not possess analogical properties. As example — derivatives of Diethyldithiocarbamic acid of Dimethyldithiocarbamic acid, aminoacids Cystein, Glutathione and Hystidine. Complexes formed by noted above protectors not contains in molecule tetragonal or pentagonal rings and not containsor contains minimal number (1–2) of double connections. Administration of large amount of these chelators not result destruction of B-cells and protect, in opposite, B-cells of destruction caused by diabetogenicchelators.

Noted above data put us to look on these chemicals as on one possible factor in ethiology of human diabetes. The significance of this possibility is increased taking consideration fact that human pancreas contains large amount of Zn-ions possess to form chelat complexes with diabetogenic chelators.

Obtained results demonstrated that Glutathione reduced form's protective activity determined by its ability to prevent formation of toxic chelate complexes with DZC due to high affinity for Zinc and more suitable for to elaborate of methods for prevention of diabetes caused by DZC synthezised in human.

### Conclusions

1. Diabetogenic zinc binding chemicals formed toxic for cells intracellular chelate salts with zinc in pancreatic B-cells by fixation of zinc atom between oxygen and nitrogen atoms, between two atoms of oxygen or between sulfur and nitrogen atoms due to high affinity of zinc for high affinity of zinc in relation to these chemical elements.

2. Non-diabetogenic zinc binders as derivatives of Dithiocarbamic acid, as well as amino acids — a Restored form of Glutathione and Cysteine formed intra-complex salts with zinc by fixation of zinc between two sulfur atoms of two molecules of the aminoacids in all cases; such complexes do not cause damage and death of B-cells, preserving their function.

### References

- 1 Scott D.A. The effect of zinc salts on the action of insulin / D.A. Scott, A.M. Fischer // Journal of Pharmacology and Experimental Therapy. — 1935. — Vol. 55. — P. 206–211.
- 2 Scott D.A. The insulin and zinc content in the normal and diabetic pancreas / D.A. Scott, A.M. Fischer // Journal of Clinical Investigations. — 1938. — Vol. 17. — P. 725–728.
- 3 Eisebrandt J. Effects on the endocrine pancreas in Chinese hamsters fed zinc deficient diets / J. Eisebrandt, M. Sienz, F. Wegel, F. Aisebrandt // Medizin und Chemie. — 1942. — Vol. 8. — P. 259–296.
- 4 Okamoto K. Diabetes Mellitus: Theory and Practice / K. Okamoto. — New York, 1970. — P. 236–255.
- 5 Andersson T. Subcellular distribution of zinc in islet's B-cells fractions / T. Andersson, P. Betgreen, P. Flatt // Hormones and Metabolism Researches. — 1980. — Vol. 12, Iss. 1. — P. 275–276.
- 6 Emdin S.O. Role of zinc in insulin biosynthesis. Some possible zinc-insulin interactions in the pancreatic B-cell / S.O. Emdin, G.G. Dodson, J.M. Cutfield, S.M. Cutfield // Diabetologia. — 1980. — Vol. 19, Iss. 3. — P. 174–182.



- 7 Okamoto K. Submicroscopic histochemical demonstration of intracellular reactive zinc in B-cells of pancreatic islets / K. Okamoto, H. Kawanishi // *Endocrinology Japan*. — 1966. — Vol. 13, Iss. 3. — P. 305–318.
- 8 Мейрамова А.Г. Диабетогенные цинксвязывающие В-цитотоксические соединения / А.Г. Мейрамова // *Проблемы эндокринологии*. — 2003. — Т. 49, № 2. — С. 8–16.
- 9 Okamoto K. Experimental pathology of diabetes mellitus / K. Okamoto // *Tohoku Journal of Experimental Medicine*. — 1975. — Vol. 61, Iss. 1–2. — P. 1–61.
- 10 Мейрамов Г.Г. Ультраструктура панкреатических В-клеток при дитизоновом диабете и его предупреждение дитиокарбаматом натрия / Г.Г. Мейрамов, Н.И. Труханов // *Проблемы эндокринологии*. — 1975. — Т. 21, № 6. — С. 92–95.
- 11 Albert A. Studies of the toxicity of chelate complexes of 8-oxyquinoline with Zn-ions / A. Albert, S. Rubbo // *Britain Journal of Experimental Pathology*. — 1947. — Vol. 28. — P. 69–70.
- 12 Albert A. Selective Toxicity / A. Albert. — London, 1968. — 431 p.
- 13 Weitzel G. Zink bindings wermogen und Blutzucker wirkung von Xanturensaure, Kynurenin und Tryptophan / G. Weitzel, E. Budecke // *Hoppe-Seyler's Journal of Physiology*. — 1954. — Vol. 298. — P. 169–184.
- 14 Meyramov G.G. Glutathione's restored Form Protect B-cells from Destruction Caused by Diabetogenic Ligands / G.G. Meyramov, A.S. Shaybek // *Diabetes*. — 2015. — Vol. 64, Iss. 1. — P. 735.
- 15 Meyramov G.G. Restored form of Glutathione protect B-cells from destruction caused by xanthurenic acid / G.G. Meyramov, A.S. Shaybek // *Diabetes Technology and Therapeutics*. — 2017. — Vol. 19, Iss. 1. — P. 127.
- 16 Meyramov G.G. Prevention destruction of pancreatic B-cells by chelators by reduced form of Glutathione / G.G. Meyramov, A.S. Shaybek // *Bulletin of the Karaganda University. Series Biology. Medicine. Geography*. — 2017. — No. 3(87). — P. 97–103.
- 17 Al-Turk W.A. Changes in glutathione, glutathione reductase and glutathione-S-transferase as a function of concentration and age / W.A. Al-Turk, S.J. Stohs, F.H. El-Rashidy, S. Othman, O. Shaheen // *Pharmacology*. — 1987. — Vol. 34. — P. 1–8.
- 18 Bravenboer B. Potential use of glutathione for the prevention and treatment of diabetic neuropathy in the streptozotocin-induced diabetic rat / B. Bravenboer, A.C. Kappelle, F.P. Hamers // *Diabetologia*. — 1992. — Vol. 35, Iss. 9. — P. 813–817.
- 19 Мейрамов Г.Г. О предотвращении развития экспериментального диабета, вызываемого цинк-связывающими веществами, с помощью аминокислоты цистеина / Г.Г. Мейрамов, К.-Д. Конерт, А.Ж. Шайбек // *Бюлл. эксперимент. биол. и мед.* — 2019. — Т. 168, № 11. — С. 559–564.
- 20 Meyramov G.G. Histochemical and Immunohistochemical Investigation of Endocrine Tissue of Pancreas after Damage Caused by B-cytotoxic Chemicals and its Prevention by L-Hystidine / Meyramov G.G., Shaybek A.S. // *Bulletin of the Karaganda University. Series Biology. Medicine. Geography*. — 2017. — No. 1(85). — P. 60–71.
- 21 Kim B-J. Zinc as paracrine effector in pancreatic islet cell death / B.-J. Kim, Y.-H. Kim, S. Kim // *Diabetes*. — 2000. — Vol. 49, Iss. 3. — P. 367–372.
- 22 Meyramov G.G. Histological Changes in Pancreatic Islets of Animals with Experimental Diabetes Caused by Xanthurenic Acid under condition of Suppression of its Endogenous Synthesis / G.G. Meyramov, A.S. Shaybek // *Bulletin of Experimental Biology and Medicine*. — 2015. — Vol. 159, Iss. 5. — P. 680–684.

Г.Г. Мейрамов, В.И. Корчин, А.Ж. Шайбек, А.П. Андреева,  
Г.О. Жузбаева, Д.А. Мейрамова, А.Г. Абдраимова-Мейрамова

### Диабетогенді уытты заттардың ұйқы безінің мырышымен өзара әрекеттесуінің химиялық механизмдері және оның алдын алу әдістері

Әдебиетке шолуда соңғы онжылдықта адаммен байланысу мүмкіндігі біртіндеп артып, химиялық мырышбайланыстырушы заттар туындататын экспериментальды диабеттің дамуын алдын алу әдістері туралы деректер келтірілген. Олардың арасында, негізгі назар бұрында маңыздылығына азырақ көңіл бөлінген глутатионның аминқышқылды топтың алдын алу бейімділік қабілеті бар екендігі ескерілген. Мақалада көрсетілгендей, глутатионның мырышына деген жоғарғы белсенділігі оның құрылымында SH-молекула топтың болуымен, осы арқылы диабетогенді емес мырыштың бұғатталуы диабетогенді хелаторлармен байланысын туындатпайды, нәтижесінде инсулин өндіруші В-жасушалары 15–30 минут шамада жойылады. Сондай-ақ, диабетогенді мырышбайланыстырушы заттар (ДМЗ) туындататын диабеттің дамуына жол бермейтін, молекула құрылымында сульфгидрильді топтардан тұратын тағы екі аминқышқылдың мүмкіндігі туралы деректер берілген. Әдебиетке шолуда мырышқа қатысты кешенді қалыптастырушы қасиеттері бар кейбір дәрілік препараттар туралы ақпараттар келтірілген.

*Кілт сөздер:* мырыш, В-жасушалар, диабетогенді мырышбайланыстырушы хелаттар, глутатион, дифенилтиокарбазон (дитизон).

Г.Г. Мейрамов, В.И. Корчин, А.Ж. Шайбек, А.П. Андреева,  
Г.О. Жузбаева, Д.А. Мейрамова, А.Г. Абдраимова-Мейрамова

## Химические механизмы взаимодействия диабетогенных токсических веществ с цинком поджелудочной железы и методы его предотвращения

В обзорной статье приведены данные о методах предотвращения развития экспериментального диабета, вызываемого химическими цинксвязывающими веществами (ДЦВ). На основе данных многолетних исследований (1964–2018) авторами детально проанализированы и обоснованы химические механизмы блокирования цинка в клетках, благодаря чему предотвращается возможность их разрушения диабетогенными цинксвязывающими веществами. По результатам собственных исследований и данных литературы изучены химические механизмы предупреждающего действия производных дитиокарбаминной кислоты, аминокислот — восстановленного глутатиона, цистеина и гистидина, а также возможности химической нейтрализации в крови ДЦС до того, как они достигнут поджелудочной железы.

*Ключевые слова:* цинк, В-клетки, диабетогенные цинксвязывающие вещества, глутатион, дифенилтиокарбазон (дитизон).

### References

- 1 Scott, D.A., & Fischer, A.M. (1935). The effect of zinc salts on the action of insulin. *Journal of Pharmacology and Experimental Therapy*, 55, 206–211.
- 2 Scott, D.A., & Fischer, A.M. (1938). The insulin and zinc content in the normal and diabetic pancreas. *Journal of Clinical Investigations*, 17, 725–728.
- 3 Eisebrandt, J., Sienz, M., Wegel, F., & Aisebrandt, F. (1942). Effects on the endocrine pancreas in Chinese hamsters fed zinc deficient diets. *Medizin und Chemie*, 8, 259–296.
- 4 Okamoto, K. (1970). *Diabetes Mellitus: Theory and Practice*. New York, 236–255.
- 5 Andersson, T., Betgreen, P., & Flatt, P. (1980). Sub cellular distribution of zinc in islet's B-cells fractions. *Hormones and Metabolism Researches*, 12(1), 275–276.
- 6 Emdin, S.O., Dodson, G.G., Cutfield, J.M., & Cutfield, S.M. (1980). Role of zinc in insulin biosynthesis. Some possible zinc-insulin interactions in the pancreatic B-cell. *Diabetologia*, 19(3), 174–182.
- 7 Okamoto, K., & Kawanishi, H. (1966). Submicroscopic histochemical demonstration of intracellular reactive zinc in B-cells of pancreatic islets. *Endocrinology Japan*, 13(3), 305–318.
- 8 Meyramova, A.G. (2003). Diabetohennye tsinksvyazyvayushchie B-tsitotoksicheskie soedineniia [Diabetogenic zincbinding B-cytotoxic chemicals]. *Problemy endokrinologii — Problems of Endocrinology*, 49(2), 8–16 [in Russian].
- 9 Okamoto, K. (1975). Experimental pathology of diabetes mellitus. *Tohoku Journal of Experimental Medicine*, 61(1–2), 1–61.
- 10 Meyramov, G.G., & Truhanov, N.I. (1975). Ultrastruktura pankreaticheskikh B-kletok pri ditizonovom diabete i eho preduprezhdenii dietilditiokarbamatom natriia [Ultrastructure of pancreatic B-cells diabetes caused by Dithizone and its prevention by Diethylthiocarbamate sodium]. *Problemy endokrinologii — Problems of Endocrinology*, 20(6), 92–95 [in Russian].
- 11 Albert, A., & Rubbo, S. (1947). Studies of the toxicity of chelate complexes of 8-oxyquinoline with Zn-ions. *Britain Journal of Experimental Pathology*, 28, 69–70.
- 12 Albert, A. (1968). *Selective Toxicity*. London, 431.
- 13 Weitzel, G., & Budecke, E. (1954). Zinkbindungswormogen und Blutzucker wirkung von Xanturensaure, Kynurenin und Tryptophan. *Hoppe-Seyler's Journal of Physiology*, 298, 169–184.
- 14 Meyramov, G.G., & Shaybek, A.S. (2015). Gluthation's restored Form Protect B-cells from Destruction Caused by Diabetogenic Ligands. *Diabetes*, 64(1), 735.
- 15 Meyramov, G.G., & Shaybek, A.S. (2017). Restored form of Gluthatione protect B-cells from destruction caused by xanthurenic acid. *Diabetes Technology and Therapeutics*, 19(1), 127.
- 16 Meyramov, G.G. & Shaybek, A.S. (2017). Prevention destruction of pancreatic B-cells by chelators by reduced form of Gluthatione. *Bulletin of the Karaganda University. Series Biology. Medicine. Geography*, 3(87), 97–103.
- 17 Al-Turk, W.A., Stohs, S.J., El-Rashidy, F.H., Othman, S., & Shaheen, O. (1987). Changes in glutathione, glutathion reductase and glutathione-S-transferase as a function of concentration and age. *Pharmacology*, 34, 1–8.
- 18 Bravenboer, B., Kappelle, A.C., & Hamers, F.P. (1992). Potential use of glutathione for the prevention and treatment of diabetic neuropathy in the streptozotocin-induced diabetic rat. *Diabetologia*, 35(9), 813–817.
- 19 Meyramov, G.G., Kohert, K.-D., & Shaibek, A.Zh. (2019). O predotvrashchenii razvitiia experimentalnogo diabeta, vzyvaemogo zinksvyazyvayushchimi veshchestvami s pomoshchiu aminokisloty tsisteina [On the prevention of developing of experimental diabetes caused by zinc binding chemicals by aminoacid Cystein]. *Bulletin of Exp. Biology and Medicine*, 168(11), 559–564 [in Russian].
- 20 Meyramov, G.G., & Shaybek, A.S. (2017). Histochemical and Immunohistochemical Investigation of Endocrine Tissue of Pancreas after Damage Caused by B-cytotoxic Chemicals and its Prevention by L-Hystidine. *Bulletin of the Karaganda University. Series Biology. Medicine. Geography*, 1(85), 60–71.

21 Kim, B-J., Kim, Y-H., & Kim, S. (2000). Zinc as paracrine effector in pancreatic islet cell death. *Diabetes*, 49(3), 367–372.

22 Meyramov, G.G., & Shaybek, A.S. (2015). Histological Changes in Pancreatic Islets of Animals with Experimental Diabetes Caused by Xanthurenic Acid under condition of Supression of its Endogenous Synthesis. *Bulletin of Experimental Biology and Medicine*, 159(5), 680–684.

Репозиторий Қарғу