UDC 616-018:616:379-008.64:577:112.

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INTERACTION OF ZINC OF PANCREATIC ß-CELLS WITH CYSTEIN AS POSSIBLE CAUSE OF ITS PROTECTIVE ACTIVITY

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It is known that zinc, contained in β-cells of the pancreas, takes an important part in the formation of its deposited storage form in the cell, due to which not all of the cell-synthesized hormone, but only a certain amount of it, enters the blood, regulating carbohydrate metabolism and providing maintenance of blood glucose level at a constant level. It is also known that there are zinc-binding diabetogenic substances that, when ingested, bind to zinc of β-cells, forming toxic complexes, leading to destruction and cell death within 15-30 minutes. A total of 18 such substances are known, and 17 of them refer to derivatives of 8-hydroxyquinoline, some of whose representatives are components of 12 drugs (in 1970 there were 2 of them). It is also known that the preliminary introduction of the amino acid cysteine completely prevents the development of diabetes caused by zinc-binding diabetogenic substances. Presumably, this is justified by its ability to block zinc in the doses used for 24-36 h, preventing it from interacting with zinc-binding diabetogenic substances. Authors using sensitive and strictly specific methods have established that indeed, cysteine blocks islet zinc, preventing its interaction with zinc-binding diabetogenic substances.

The authors believe that the blocked zinc atoms are fixed between the sulfur atom that is part of the SH group in the cysteine molecule and the oxygen atom of the carboxyl group, or between the sulfur atom and the nitrogen atom of the amino group of the cysteine molecule, as is also the case with the interaction of zinc with zinc-binding diabetogenic substances, where chelates with zinc are formed only as a result of fixing them between these atoms.

Key words: diabetes, cysteine, zinc-binding diabetogenic substances, cell

Pancreatic islets of many mammals as rabbits, dogs, cats, pigs, mice, horses, hamsters and of human contains a large amount of ions of zinc [1, 2, 3]. In ß-cells Zn^{+2}-ions take part in processes of biosynthesis of insulin as in processes of storage by forming of Zn^{+2}-insulin complex concentrated in B-cells [4, 5]. It is known that Zn^{+2}-ions in ß-cells formed with insulin a deposited form as Zn^{+2}-insulin complex [5]. In addition the Zn^{+2}-ions increase solubility of proinsulin. It is known a group of diabetogenic chemicals [1, 2, 3, 6, 7, 8, 9] capable for selective alteration and death ß-cells. 17 from this group are belong to Zn^{2+}-binding derivatives of 8-hydroxyquinolin (DZS) and formed in ß-cells of complexes salts with zinc that result destruction of ß-cells and death within short period [8]. It was confirmed that all causes prevented interaction of zinc in B-cells with DZS protect ß-cells from destruction [1, 2, 7, 8].

Previously it was reported that amino acid Cystein are able to prevent from developing of diabetes in animals [10, 11]. It was supposed that protective ability is determined by ability to form not toxic salts with ß-cells that result prevention destruction of cells caused by DZS. Meanwhile now this problem is not cleared because it not investigated possible interaction of zinc in B-cells with Cystein.

The aim of work is to investigate possibnsulinle interaction of zinc in pancreatic B-cells with Cystein

MATERIALS AND METHODS

Reagents: 8-p-toluenesulphonamido-quinoline (8PTSQ) was from Institute of Pure Reagents (Moscow, Russia), Dithizon from MERCK (Germany).

DZS were used to induce experimental diabetes of 2 type. Diphenylthiocarbazon (DZ) and 8 -p-toluenesulphonamido-quinoline (8PTSQ) possess two important properties for this purpose: 1) to form with zinc in β-cells chelat complexes highly specific for zinc; 2) complexes with (8PTSQ) have bright green fluorescence [1, 2, 7, 8, 9] that allows to observe visually of zinc in β-cells and estimate content by measuring of intensity of fluorescence by using of fluorescent microscopy; 3) complexes of zinc with Dithizon revealed in cells as bright red granules using of dark microscopy. Both complexes at the same time are toxic for β-cells and after intravenous injection of 8PTSQ and of DZ result destruction and death of the majority of β-cells and developing of type 1 diabetes mellitus. High specificity of Dithizon for identification of zinc confirmed by results of comparative spectral analysis of spectrum of absorb-

ance of complex Zn^{+2}-Dithizon extracted from B-cells with the similar artificial complex formed in vitro. The maximum of absorption of both ranges was identical and made 530 nanometers [7].

16 rabbits weighing 2240-2680 g were divided for 2 groups: 1) injection of DZ, 48,9-52,4 mg/kg; 2) injection of Cystein, 955-1000 mg/kg+10 min later injection of DZ, 49,3-50,4 mg/kg; all animals were killed 6-8 min after injection of DZ.

Preparing of Dithizon solution: 30 ml of distilled water added 0,6 ml of 25% of solution of ammonia, 400 mg of Dithizon. Mixing on water bath (+70 °C) for 10 min. Preparing of solution of 8PTSQ: 25 mg. powder 8PTSQ (Institute of high pure rea- gents, Moscow, Russia) dissolved in 70% ethanol at a temperature + 70^0C; mixing within 10 min. on a water bath then injected intravenously of 38-42 mg/kg. 8PTSQ formed fluorescent complexes with zinc and cadmium. But cadmium is absent in pancreatic β-cells. That is why 8PTSQ for β-cells is high specific for staining of zinc ions [12]. The complex Zn^{+2}-8PTSQ in ultraviolet light at of 360-370 nm fluoresces bright green light. Method is high sensitive for revealing of zinc concentration as 10^{-7}-10^{-8}. The reagent was offered by Institute of High Pure Reagents (Moscow) as high specific method for revealing of zinc-ions in tissues of animals, including pancreas tissue [12, 13, 14].

Frozen sections 4-5 mcm of pancreas of animals were investigated using dark-field microscopy after intravenous administration of Dithizon and of luminescent microscopy for histochemical luminescent identification of zinc in β-cells after staining of sections of pancreas tissue by 8PTSQ or after intravenous injection of 8PTSQ 0,4% aceton solution of 8PTSQ was used: several drops of which applied on sections for 10-12 sec.; washing of sections later by distilled water.

Zinc content in ß-cells was estimated using of histofluorimetric method in the relative units (r. e.) by measuring intensity of fluorescence of complex Zn^{+2}-8PTSQ in β-cells and of density of concentration of granules of Zn^{+2}-Dithizon [15, 16] by calculation of parameter "K" based on direct dependence between intensity of a fluorescence (8PTSQ) and of density of staining (Dithizon) of β-cells and content of zinc. Calculation of parameter K for a 8PTSQ-luminescent method of identification of Zn^{+2}-ions in β-cells: IF1/IF2, where: IF1- luminescent emission of B-cells, and IF2-intensity of luminescence of exocrine tissue (absence of color, as 1.00). Calculation of parameter K for Dithizon method of identification of Zn^{+2}-ions in β-cells: AF1/AF2, where: AF1-density of staining of β-cells and AF2 -density of staining of exocrine tissue (absence of color, as 1.00).

RESULTS AND DISCUSSION

Obtained results demonstrate that a large amount of Zn^{+2}-ions are concentrated in pancreatic B-cells of intact rabbits (table 1). In sections of pancreas of animals of group 1 show positive Dithizon reaction for zinc in the form of red granules of Zn^{+2}-Dithizon complex (fig. 1.3) filling cytoplasm of β-cells comparatively absence of complex in intact animals (fig. 1.1). Similar results obtained using of 8PTSQ reaction: a large amount of zinc in β-cells of intact animals - the intensive bright green luminescence of a complex Zn^{+2}-8PTSQ (fig. 1.2) in compared with expressed negative reaction in β-cells of animals of groups 2 after administration of Cystein and DZ (fig. 1.4, 1.6, table 1) was observed. Negative fluorescent reaction for zinc with 8PTSQ after injection of Cystein and DZ determined by binding zinc by DZ and by Cystein as negative reaction for zinc using DZ method in sections of animals after administration of Cystein (fig. 1.5, 1.6) determined by binding of zinc with Cystein in compared with positive reaction in intact animals (fig. 1.1).

Diabetogenic derivatives of 8-oxyquinolin contains in the 8 position of quinolin ring active OH^- radical or other radicals contains atoms of S, N or O. Six isomers of 8-oxyqunolines not contains in this position of such radicals or atoms or if these radicals were extracted from molecule – not able to form complex salts with zinc and not possess diabetogenic properties [6, 17]. It is necessary to return active radicals in position 8 for to restore diabetogenic activity of substance [6, 17]. Formation of the chelatcomplex via atoms of O and N result formation of pentagon or hexagon rings [6].

It is known that in process of formation of the Zn^{+2}-complex with diabetogenic derivatives of 8-oxyquinolin and Dithizon atom of zinc is fixed between S or O atoms in position 8, and N or O atoms - in positions 1 or 2 (fig. 2). Padding durability to the Zn-DZ complex is determined by fixation Zn atom between not one, but between two atoms of S and two atoms of N of two molecules of dithizon. In molecule of Cystein evidently atom of Zn should be fixed between S atom from the SH radical and, most likely, atom of O of carboxyl group (fig. 2). Logarithm of a constant of stability of complex is high as 8,5. G. Weitzel et al. [18] confirmed that the complex 1:1 contains 1 molecule of 8-oxyquinolin and 1 atom of zinc is most toxic for cells.

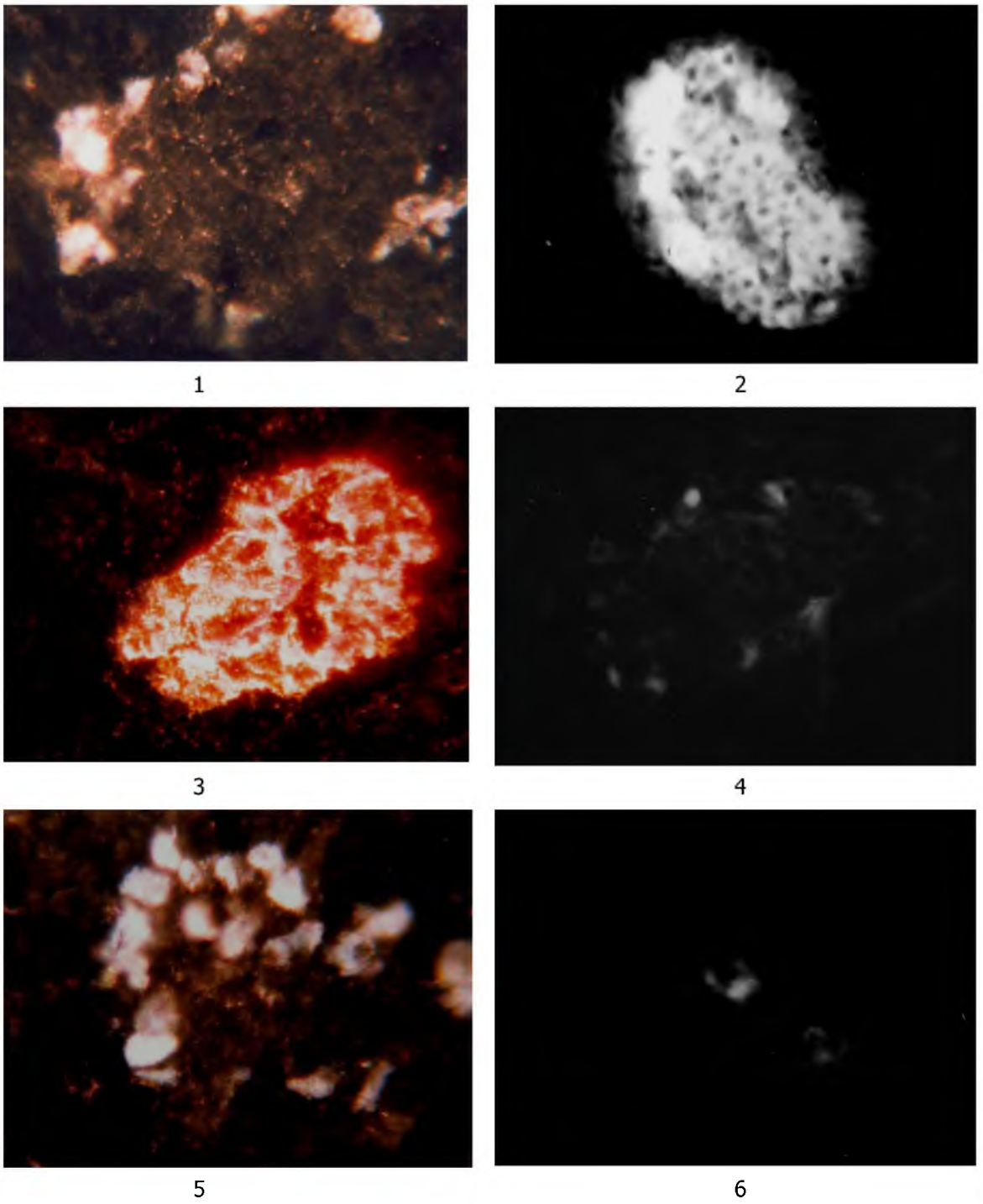
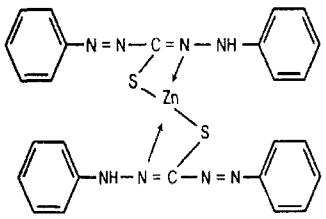


Figure 1 – Interaction of DZ and 8PTSQ with zinc ions in pancreatic B-cells. 1.1 – Pancreas of intact rabbit. Frozen section. Dark microscopy; x280; 1.2 – Rabbit. Pancreas of intact rabbit. Frozen section. Positive fluorescent reaction for zinc-ions. 8PTSQ reaction; fluorescent microscopy; x140; 1.3 – Injection of DZ , 49,3 mg/kg. Positive reaction for Zn^{+2}-ions in B-cells – a large amount of red granules of complex DZ-Zn in B-cells; dark microscopy; x280; 1.4 – Injection of DZ , 49,3 mg/kg; negative reaction for Zn^{+2}-ions in B-cells with 8PTSQ: zinc in B-cells is connected with DZ; fluorescent microsco-py; x140; 1.5 – Injection of Cystein, 976 mg/kg+DZ, 48,8 mg/kg; negative reaction for zinc with DZ as result of binding of zinc with Cystein; darc microscopy; x280; 1.6 – Injection of Cystein, 976 mg/kg+DZ, 48,8 mg/kg; negative reaction for zinc with 8PTSQ as result of binding of zinc with Cystein; fluorescent microscopy; x140

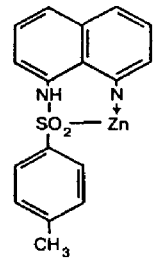
Table 1 – Zinc ions content in pancreatic β-cells in animals after administration of DZ and Cystein (relative units (r. e.)

Group	Experimental conditions	Insulin content in pancreatic β-cells (r.e.)	
		8-TSH reaction (zinc) (IF1/IF2)	Dithizon reaction (zinc) (AF1/AF2)
1	Intact rabbits	2,04±0,08 (n=22)	1,02±0,04 (n=20)
2	DZ	1,02±0,04 (n=16)	1,95±0,07 (n=18)
3	GRF+DZ	1,02±0,04 (n=20)	1,03±0,03* (n=23)
4	GOF+DZ	1,05±0,04 (n=21)	1,92±0,06* (n=18)

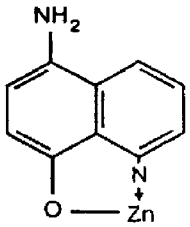
*p<0,001; n – number of measurements



Dithizon

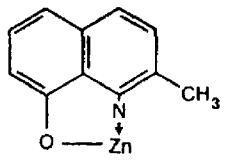


8-TSH

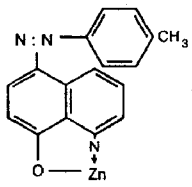


5-amino-8-oxyquinolin

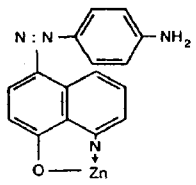
Cystein



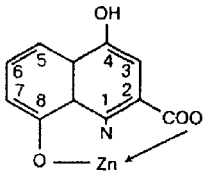
8-oxyquinaldine



5-para (toluene)-8 - oxyquinolin



5-para (aminophenylaso) - 8-oxyquinolin



4,8 –dihydroxyquinolin-2-carboxylic acid (xanturenic acid)

Figure 2 – Structure of zinc complexes with DZ and Cystein

High durability of the Zn^{+2}-Dithizon complex 2:1 (fig. 2) determined by space elongation of molecule of Dithizon and disposition of two phenolic rings on the ends of a molecule that does not prevent the atoms of S and N located in the center of a molecule to approach zinc atom. Besides, atom of zinc is located between two atoms of N and S, regarding to which affinity of zinc is very high and exceeds affinity to O. At last, two molecules of Dithizon having totally larger number double connections increases toxicity of the Zn^{+2}-Dithizon complex.

Pentagonic rings are evidently more stable. In case if atoms of S participate in formation of chelates and then most stable are quadrangular rings (fig. 2). Electrons of the lone pair of electrons are displaced from N-donor-atom located in the first position to Zn-atom. In experiences with various isomers of 8-oxyquinolin there are dependence according to which the maximal toxicity possess isomers which are forming chelates of structure 1:1 with metal and have a stability constant logarithm equal 7,6 - 9,4 [6]. The complexes of derivatives of 8-oxyquinolin possess high toxicity for B-cells formed with Zn have a high rate of logarithm of a constant of stability, equal 8, 5. G. Weitzel et al. [18] confirmed that the complex of structure 1:1 contains 1 molecule of 8 -oxyquinolin and 1 atom of zinc is most toxic for ceiis.

Earlier it was shown that amino acid Cystein is able to prevent destruction of B-cells [19] by not diabetogenic binding of Zn in cells as well as Glutathione. In the structure of Cystein

SH radical is located nearby atom of N from NH_2 radical. Meanwhile, it is known that forming complexes of Zn its atom most often is fixed between atom of S, N and O. In molecule of Cystein the radicals containing these atoms are located near.

Meanwhile, it is reason to note that number of current pharmaceuticals drugs contains in chemical structure a derivatives of 8-hydroxyquinolin is increased now to more than 10 drugs: Ketotifen, Intestopan, Enteroseptol, Nitroxolin (5NOK), Mexase, Chinosolum, Chlorchinaldolum, Mexaform and Salmeterol are belong to this group [20, 21]. Therefore it is necessary to keep attention to this group of chemicals as one of potentially possible cause of developing of diabetes.

CONCLUSION

1. Injection to animal of Cystein, 955-1000 mg/kg is followed by completely negative reaction for zinc in B-cells as result of binding of zinc; followed injection of DZ not accompanied by formation of complex DZ-zinc

2. We suppose that zinc atom is fixed between atom of S and of atom O from car- boxyl radical of molecule of Cystein.

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Received 11.01.2018

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ВЗАИМОДЕЙСТВИЕ ЦИНКА ПАНКРЕАТИЧЕСКИХ ß-КЛЕТОК С ЦИСТЕИНОМ КАК ВОЗМОЖНАЯ ПРИЧИНА ЕГО ЗАЩИТНОГО ДЕЙСТВИЯ

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Известно, что цинк, содержащийся в β-клетках поджелудочной железы, принимает важное участие в образовании его депонированной формы хранения в клетке, благодаря чему не весь синтезированный клеткой гормон, а только определенное его количество по мере необходимости поступает в кровь, регулируя обмен углеводов и обеспечивая поддержание уровня глюкозы крови на постоянном уровне. Известно также, что существуют цинксвязывающие диабетогенные вещества, которые при попадании в кровь связываются с цинком β-клеток, образуя токсичные комплексы, приводящие к разрушению и гибели клеток в течение 15-30 мин. Всего таких веществ известно 18, и 17 из них относятся к производным 8-оксихинолина, отдельные представители которых являются компонентами 12 лекарственных препаратов (в 1970 г. их было 2). Известно также, что предварительное введение аминокислоты цистеина полностью предовращает развитие диабета, вызываемого цинксвязывающими диабетогенными веществами. Предположительно это обосновывается ее способностью в использованных дозах на 24-36 ч блокировать цинк, не давая ему возможности взаимодействовать с цинксвязывающими диабетогенными веществами. Авторами с помощью чувствительных и строго специфичных методов установлено, что действительно, цистеин блокирует островковый цинк, предотвращая его взаимодействие с цинксвязывающими диабетогенными веществами.

Авторы считают, что блокируемые атомы цинка фиксируются между атомом серы, входящим в состав SH-группы в молекуле цистеина, и атомом кислорода карбоксильной группы, либо между атомом серы и атомом азота аминогруппы молекулы цистеина, как это имеет место и при взаимодействии цинка с цинксвязывающими диабетогенными веществами, где хелаты с цинком формируются только в результате фиксации их между этими атомами.

Ключевые слова: диабет, цистеин, цинксвязывающие диабетогенные вещества, клетка

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ПАНКРЕАТИЯЛЫҚ ß-КЛЕТКАЛАРДЫҢ МЫРЫШЫНЫҢ ЦИСТЕИНМЕН ӨЗАРА ӘРЕКЕТІ ОНЫҢ ҚОРҒАНЫС ӘРЕКЕТІНІҢ МҮМКІН СЕБЕБІ РЕТІНДЕ

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Өттің β-клеткалары құрамындағы мырыш клеткада сақтаудың депондалған формасына қатысуда маңызды оырн алады, нәтижесінде гормондардың барлық синтезделген клеткасы емес, тек оның белгілі бір саны қажетіне қарай қанға түседі, осылайша көмір қышқылының алмасуын реттейді және қан глюкозасын тұрақты деңгейде ұстауды қамтамасыз етеді. Сол сияқты мырыш жалғаушы диабетогенді заттар бар екені белгілі, олар қанға түскен кезде β-клетка мырышымен байланысады, осылайша токсикалық кешендер құрып, салдарынан клетканың 15-30 минут ішінде бұзылуы мен өлуіне әкеледі. Барлығы осындай 18 зат белгілі, оның 17-сі 8-оксихинолиннің өніміне жатады, жекелеген өкілдері 12 дәрілік препараттардың компоненттері болып табылады (1970 жылы олар 2 болған). Сол сияқты цистеин амин қышқылын алдын ала енгізу мырыш жалғаушы диабетогенді заттар тудыратын диабеттің дамуының толық алдын алатыны белгілі болған. Алдын ала болжамға қарағанда, бұл 24-36 оның сағаттарда пайдаланылатын дозаларында мырышты блоктау, оған мырыш жалғаушы диабетогенді заттармен өзара әрекет ету мүмкіндіктеріне жол бермеу қабілетіне негізделеді. Авторлар сезімтал және қатаң спецификалық әдістермен цистеин аралық мырышты блоктайтынын, сол арқылы оның мырыш жалғаушы диабетогенді заттармен өзара әрекет етуінің алдын алатынын анықтаған.

Авторлар мырыштың блокталатын атомдары цистеин молкулы SH-тобына кіретін күкірт атомы мен карбоксилді топтың считают кислород атомы,немесе күкірт атомы мен цистеин молекулының аминотобының азот атомы арасында мырыш жалғаушы диабетогенді заттардың өзара жалғаушы әрекеттері бар деп санайды. Онда хелаттар мырышпен тек осы атомдар арасындағы фиксация кезінде жасақталады.

Кілт сөздер: диабет, цистеин, мырыш жалғаушы диабетогенді заттар, клетка