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G.G.Meyramov[1, 2], K.-D.Kohnert[1, 3], L.Vogt[3, 4], Z.T.Kystaubaeva[2], G.M.Tykezhanova[2], G.T.Tusupbekova[4], F.A.Mindubaeva[5], G.O.Zhuzbaeva[2], A.S.Shaybek[2], Z.Z.Zhumagalieva[2], S.S.Tyrzhanova[2], K.A.Zhumasheva[2], A.Kaibogarova[5]

[1]Diabetes Research Group, Karaganda;
[2]Karaganda State University;
[3]Institute of Diabetes «Gerhardt Katsch», Karlsburg, Germany;
[4]Diabetes Service Centre, Karlsburg, Germany;
[4]Pavlodar Innovative University;
[5]Karaganda State Medical University
(E-mail: meyramow@mail.ru)

On the protective effect of 2,3-dimercaptopropanol for destructive action of zincbinding chemicals on pancreatic B-cells

2,3-Dimercaptopropanol is a substance able to re-activate sulfhydryl groups of enzymes and has the property to form temporary complexes with metals, including zinc. It is also known that certain amino acids, particularly cysteine and glutathione also contain in its composition mole coli SH-groups. Administration of these amino acids in to animals result prevention developing of experimental diabetes caused zinkbinding diabetogenic chemicals. It is confirmed that this effect is determined by their ability to form non-toxic temporary complexes with zinc in B-cells of pancreatic islets that protect cells of the destruction caused by diabetogenic chelating agents. The authors have shown that 2,3-dimercaptopropanol at doses of 60 and 120 mg/kg is able to prevent the development of diabetes in almost all experimental animals. Authors found that this ability 2,3-dimercaptopropanol is explained by its property through SH-groups included in its composition, to form non-toxic complexes with zinc in pancreatic cells that protect cells of death.

Key words: B-cells, SH-groups, experimental diabetes, zinc, 2,3-dimercaptopropanol.

2,3-Dimercaptopropanol (DMP) is known as re-activator of SH-group of enzymes and possess ability to form stable complexes with metals. However it is known that some aminoacids contains SH-groups in molecule as Cystein and Glutathuone reduced form protect developing of diabetes caused by chelat active chemicals. This effect determined by high affinity of SH-group for zinc and cadmium [1]. 2,3-Dimercaptopropanol is able in added to destroy other complexes, previously formed with zinc by chelators, that accompanied by re-placing atom of chelator from complex [2] and formation of complex DMT-metal via SH-group.

Aim of work: to investigate state of histostructure of pancreatic islets and possible interaction of Zn^{+2}-ions in B-cells with DMP and Dithizon, a diabetogenic chelator.

Material and methods

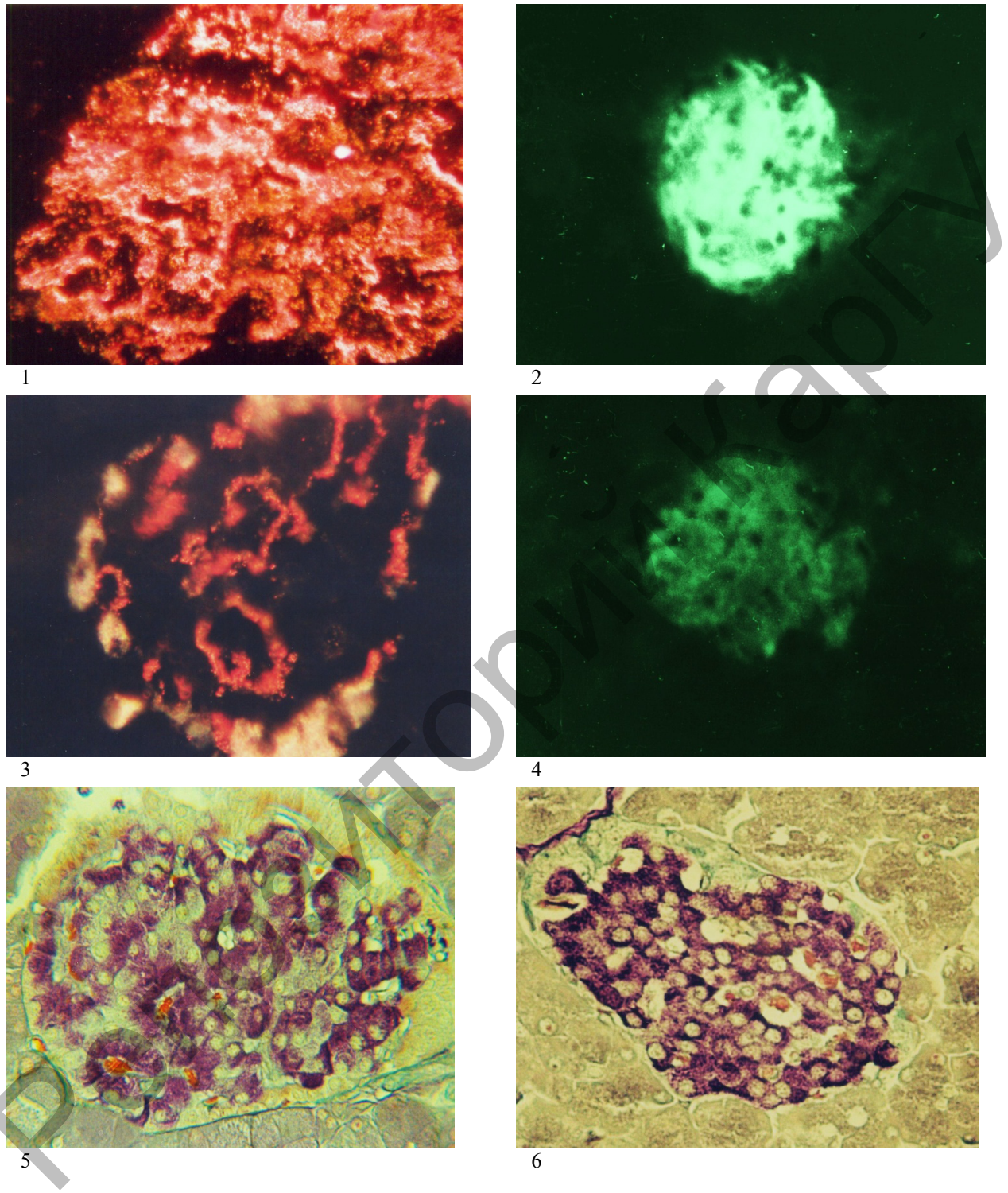
Animals: 10 rabbits 2,200–2,650 g were used. Group 1: control intact animals: A-injection of Dithizon, 48,9 mg/kg; B-intact rabbit; Group 2: injection of DMP («SIGMA») in doses 60 and 120 mg/kg to 8 animals; 30 min later water solution of Dithizon 46,6–49,7 mg/kg was injected to 6 animals; animals killed 10 min past injection of DZ. Group 3: injection of DMP, 60 and 120 mg/kg to 2 animals; animals killed 10 min past injection. Group 4**:** injection of DMP, 60 and 120 mg/kg to 2 animals; 30 min later injection of Dithizon 48 mg/kg; animals killed 5 days past injection of DZ.

Frozen sections of pancreas were investigated using dark microscopy for revealing of DZ-Zn^{+2}-complex in B-cells. The high specific fluorescent method revealing of free Zn^{+2}-ions in B-cells by fluorochrom 8-para(toluenesulphonylamino)quinolin [8PTSQ] was used [3, 4]. 3 animals were killed 5 days past injections of DMP and DZ. Pancreas was fixed in alcohol 70º + H_2S. Staining of sections by aldehyde-fucshine [5–7] and 8PTSQ.

Results

Group 1. Control intact animals section o pancreas. 20 frozen sections of pancreas tissue were investigated using dark microscopy. Cytoplasm of all investigated islets contain a large amount of red chelat complex Zn^{+2}-Dithizon [1] which concentrated on the all surface of cytoplasm, maximally around blood islet's capillaries (fig. 1.1). Reaction for Zn^{+2}-ions: intensive fluorescence of B-cells (fig. 1.2). Group 2. Administration of 2,3-dimercaptopropanol and of Dithizon result prevention of formation in majority of B-cells of Zn^{+2}-Dithizon complex which is partially formed in cells located around blood capillaries (fig. 1.3). Pro-

tective effect determined by not diabetogenic binding of Zn^{+2}-ions by DMT. It is known that DMT possess high affinity for Zn^{+2}-ions.



1 Intact rabbit. Injection of Dithizon, 48,9 mg/kg; dark microscopy; red granules of complex zinc-DZ in B-cells; [×280]
2 Intact rabbit. Positive fluorescent reaction for Zn in B-cells: intensive green fluorescence of Zn in cytoplasm of B-cells; [×140]
3 Injection of DMP 60 mg/kg + DZ; dark microscopy; only B-cells contacted with capillaries contain complex zinc-DZ; [×280]
4 Injection of DMP 60 mg/kg + DZ; negative fluorescent reaction for Zn in B-cells: only a few cells contain a small amount of Zn; [×140]
5 Dithizon, 48 mg/kg. Aldehyde-fucshine staining; destruction of B-cells; degranulation, decreasing of insulin content in B-cells; [×280]
6 Injection of DMP + DZ; Aldehyde-fucshine staining; histostructure of islets and insulin content in B-cells without changes; [×280]

Figure 1. Pancreas tissue

Group 3. Investigation of free Zn^{+2}-ions content in B-cells past injection of DMT showed a negative reaction for Zn^{+2} in islets (fig. 1.4). A few B-cells contains minimal amount of Zn^{+2} in cytoplasm. This result determined by forming by DMT of not visible Zn^{+2}-DMT complex.

Group 4. Investigation of effect of DMT on diabetogenic property of Dithizon showed that administration of it accompanied by absence of any histological changes in pancreatic islets (fig. 1.5; 1.6).

Table

Results of investigation of blood glucose level

№	Conditions	Blood Glucose (mmol/l), day				
		Before	1	3	6	7
1	Dithizon, 46,8–48 mg/kg 2 animals	5,1±0,3	3,0±0,4	9,6±1,2■	12,6±2,2●	16,2±2,6*
2	DMT, 102–110 mg/kg + Dithizon, 48,8 mg/kg, 4 animals	4,9±0,4	5,2±0,4	5,6±0,5■	5,8±0,7●	5,4±0,6*

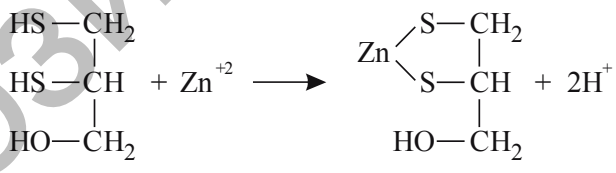
Note. * — p< 0,001; ● — p < 0,005; ■ — p < 0,01.

Results of investigation of blood glucose level (table 1) demonstrated that injection of Dithizon accompanied by marked decreasing of blood glucose level that is determined by release of a large amount of insulin as result of destruction within short time of majority B-cells. In other animals, past injections of DMT and followed past 1, 2 and 3 h injections of diabetogenic doses of Dithizon not accompanied by hyperglycemia in animals. We observed only not reliable increasing of blood glucose level until 5,6–5,8 mmol/l (Table).

Discussion

Molecule of 2,3-Dimercaptopropanol ($C_3H_8OS_2$ m.m. 124,22) contains two SH-groups**.** It is known that some metals (Me) as mercury, arsenic, cadmium, lead, zinc interacted with chemicals contains SH-groups and formed stable cyclic mercaptide:

As bivalent metal Zn^{+2}-ions interacts with 2 SH-groups of molecule of 2,3-Dimercaptopropanol with forming of cyclic mercaptide which are more stable in compared with some chelat active chemicals. It is known that 2,3-Dimercaptopropanol is able to destroy complexes previously formed with chelators accompanied by replace atom of chelator from complex [2].



Thus, obtained results showed that 2,3-Dimercaptopropanol protect B-cells of destruction caused by Dithizon and of developing of diabetes. Investigation of interaction in B-cells between Zn^{+2}-ions and 2,3-Dimercaptopropanol evidently showed that DMT protect B-cells of formation of toxic Dithizon-Zn^{+2} complex by interseption of Zn^{+2}-ions and forming new complex DMT-Zn^{+2}.

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Ғ.Ғ.Мейрамов, К.-Д.Конерт, Л.Фогт, З.Т.Қыстаубаева, Г.М.Тыкежанова, Г.Т.Түсіпбекова, Ф.А.Миндубаева, Г.Ө.Жүзбаева, А.Ж.Шайбек, Ж.Ж.Жұмағалиева, С.С.Тыржанова, К.А.Жұмашева, А.Қайбоғарова

Диабетогенді мырыш байланыстырушы қосылыстармен туындайтын панкреатит В-жасушаларының бұзылуын болдырмауда 2,3-димеркаптопропанолдың қабілеті туралы

2,3-Димеркаптопропанол өзінің молекулалық құрамында екі сульфгидрильді топ (SH-топ) болуымен, сульфгидрильді фермент тобы реактиватор ретінде белгілі және оның SH-тобы арқылы байланысатын ауыр металдармен уақытша кешен түзуге бейімді. Сонымен қатар құрамында SH-тобы бар L-гистидин және цистеин аминқышқылдары В-жасушаларының Zn^{+2} ионымен уақытша байланыстыруға бейімді, осылайша диабетогенді мырыш байланыстырушы қосылыстармен өзара әрекетіне және жойылуын болдырмауға әрекет етеді. Авторлар көрсеткендей, жануарларға 2,3-димеркаптопропанол 60 және 120 мг/кг мөлшерде енгізу В-жасушалардағы мырышты толық тоскауылдатады. 2,3-Димеркаптопропанол превентивті әрекеті оның құрамында сульфгидрильді топ молекулаларының бар болуымен сипатталады деген қорытынды жасалды.

Г.Г.Мейрамов, К.-Д.Конерт, Л.Фогт, З.Т.Кыстаубаева, Г.М.Тыкежанова, Г.Т.Тусупбекова, Ф.А.Миндубаева, Г.О.Жузбаева, А.Ж.Шайбек, Ж.Ж.Жумагалиева, С.С.Тыржанова, К.А.Жумашева, А.Кайбогарова

О способности 2,3-димеркаптопропанола предотвращать разрушение панкреатических В-клеток, вызываемое диабетогенными цинксвязывающими соединениями

2,3-Димеркаптопропанол является веществом, способным реактивировать сульфгидрильные группы ферментов и обладает свойством формировать временные комплексы с металлами, включая цинк. Известно также, что некоторые аминокислоты, в частности, цистеин и глютатион также содержат в составе своей молекулы SH-группы. Эти аминокислоты при парентеральном введении предотвращают развитие экспериментального сахарного диабета, вызываемого цинксвязывающими диабетогенными веществами. Доказано, что этот эффект обусловлен их способностью формировать нетоксичные временные комплексы с цинком В-клеток панкреатических островков, защищая их таким образом от разрушающего воздействия диабетогенных хелатообразователей. Авторами показано, что 2,3-димеркаптопропанол в дозах 60 и 120 мг/кг способен предотвращать развитие диабета почти у всех опытных животных. Авторами установлено, что эта способность 2,3-димеркаптопропанола обусловлена его свойством через SH-группы, входящие в его состав, формировать нетоксичные комплексы с цинком панкреатических В-клеток, препятствуя этим повреждающему действию диабетогенных цинксвязывающих веществ.

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