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# On the methods for prevention by aminoacids of developing of diabetes induced by chelat active chemicals

In article are presented data on methods of prevention developing of experimental diabetes caused by chemical diabetogenic zinc binding substances (DZS) as about of possibilities for contact with which of human for the last years gradually increase. Among them the main attention is fixed on ability of aminoacid of glutathione to prevent diabetogenic action of this group of substances. It is showed that the high affinity of glutathione for zinc determined by presence in structure of its molecule of SH-radical which protect by blocking of atom of zinc in B-cells of interaction of it with DZS accompanied by formation of complexes DZS that result destruction and death of pancreatic B-cells within 15–30 min. Also are presented data about ability of two other aminoacids contains sulfhydryl groups in structure of a molecule to prevent development of diabetes caused by DZS as data on the some drugs possess high affinity and chelat properties for zinc.

*Keywords:* B-cells, diabetogenic zinc binding chemicals, glutathione, insulin, zinc, experimental diabetes, glutathione reduced form, glutathione oxidised form, diphenylthiocarbazone (Dithizon), derivatives of 8-oxyquinolin.

## *Abbreviations*

DZS — Diabetogenic zinc binding chemicals;
DZ — Diphenylthiocarbazone (Dithizon);
GRF — Glutathione reduced form;
GOF — Glutathione oxidised form.

## *Background*

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 by these authors in 1938 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 1 g of pancreas tissue of diabetic patients comparatively with 0.14 mg per 1 g pancreas of healthy persons. Analogical result was obtained by Eisenbrandt and coll. [3]. A large amount of $Zn^{+2}$-ions was found in human pancreas of healthy men. K. Okamoto discovered in pancreatic B-cells a large amount of $Zn^{+2}$ [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 cristallization of insulin. It was showed that pancreas of mammals-animals, birds and in earth-water animals contained a large amount of Zn-ions.

The amount of $Zn^{+2}$ is evidently decreased in experimental diabetes induced by any causes [4]. $Zn^{+2}$ is able to be accumulated in pancreas tissue. Administration of $Zn^{+2}$ in organism accompanied by increasing of total amount in pancreas in 4–20 times. 0.3 % of $Zn^{+2}$ administrated in organism was accumulated in pancreas of alloxan diabetic rats comparatively with 2.6 % in healthy animals. H. Kawanishi and K. Okamoto by aid of electron histochemical microscopy confirmed that in B-cells Zn-ions are located in B-granules, a deposited form of insulin [7]. S. Yokoh and coll. showed that $Zn^{+2}$ is concentrated in central part of B-granules, in periphery and partly in cover of granules.

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 chelats is evidently more high comparatively with other metals of main group.

*Diabetogenic activity of zinc binding chelators dithizon and derivatives of 8-oxyquinoline*

Dithizon (diphenylthiocarbazon) is one of most active chelators [4, 9]. Dithizon formed various modifications of red colour chelats with 18 metals. It possess a marked high affinity to Zn-ions and formed very rapidly past injection chelat 2:1 that accompanied by destruction and death of B-cells within 15–30 min. and developing of 1st type of diabetes 48–72 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.

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. We 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 chelat complex in cytoplasm of B-cells.

Thus, it was concluded that destruction of B-cells past injection of diabetogenic doses of dithizon is determined by destructive action of complex Zn-DZ on structures, for the first — B-granules of B-cells, within first 15–20 min. past forming of complex in cytoplasm of B-cells.

*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 chelat metal-complexes which are toxic for B-cells [11, 12] as complexes formed in B-cells by other chelat active substance as dithizon. Studying of toxicity of 8-oxyquinolin 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-oxyquinolin 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 quinolin ring OH-group or any other radical contained atom of S or atom of O. Six isomers of 8-oxyquinolin not contained in position 8 of the active group are not able to form chelat complexes with Zn-ions and not induced experimental diabetes. Experimental diabetes is induced by derivatives as 8-para(toluenesulphinylamino)quinolin /8PTSQ/, 8-para(benzolsulphonylamino)quinolin /8PBSQ/, 8-para(methansulphonylamino)quinolin /8PMSQ/ 5-para(acetaminophenylaso)-8-oxyquinolin /5A8OX/, 8-hydroxyquinaldin, 5-amino-8-hydroxyquinolin and others (Fig. 1). It was demon strated (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.

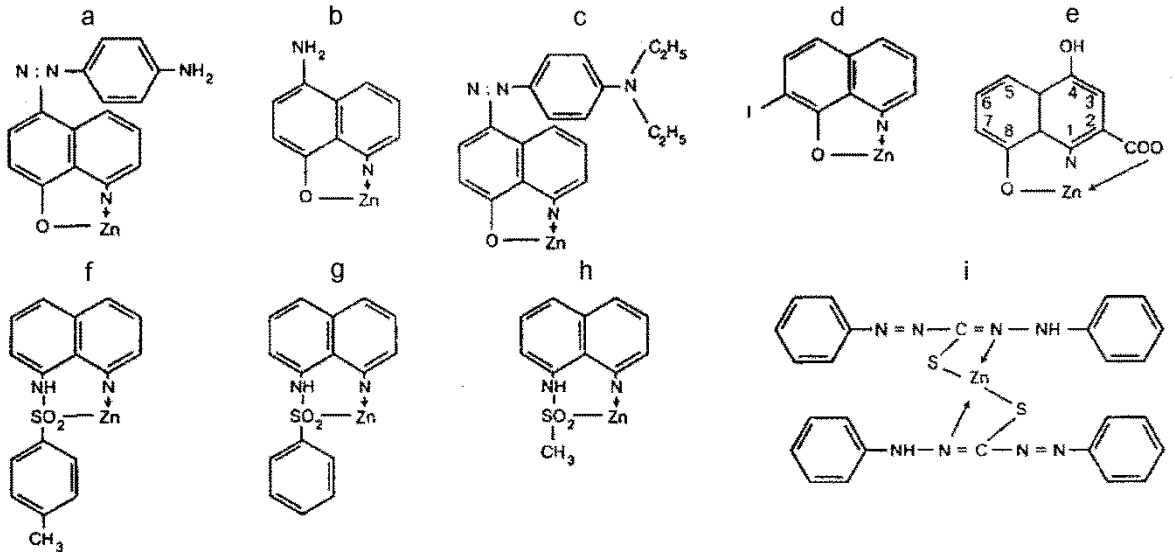
It is known that most stable complexes are formed when atom of Zn is fixed between 2 atom of N, S and O of molecule of chelator. Later it was reported that only derivatives of 8-oxyquinolin contained in position 8 of quinolin ring of the hydroxyl or other radical contained atoms of S, N or O possess diabetogenic properties. Atom of Zn is fixed between atoms of S and O in position 8 and between atoms of N and O in position 1 or 2.

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. 1). Pentagonal rings are more stable. The most stable are quadrangular complexes with atom of S. It is known that derivatives of 8-oxyquinolin formed quadragonal complexes with atom of S often. 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-oxyquinolin 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.

Finally, S. Rubbo and A. Albert established that toxic effect of 8-oxyquinolin 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 chelat a short time in cytoplasm of B-cells accompanied by alteration of cells. In experiences

with using derivatives of 8-oxyquinolin — a various isomers of the azaoxyquinolin (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 was clearly more less [11]. It was showed that very toxic chelats of derivatives of 8-oxyquinolin with Zn-ions have a more high logarithm of constant of stability as 8.5. G. Weitzel and coll. showed that complex 1:1 contained 1 molecule of 8-oxyquinolin and 1 atom of ion of Zn is most toxic for cells [13].




*a* — 5-para(aminophenylaso)-8-oxyquinolin, 10 mg/kg; *b* — 5-amino-8-oxyquinolin, 30 mg/kg;
*c* — 5-para (diethylaminophenylaso)-8-oxyquinolin, 40 mg/kg; *d* — 9-oxy-7-jodoquinolin, 50–60 mg/kg;
*e* — 4,8–dihydroxyquinolin-2-carboxylic acid (xanthurenic acid); *f* — 8-para(toluenesulphonylamino)quinolin, 30–50 mg/kg; *g* — 8-para(benzolsulphonylamino) quinolin, 30–100 mg/kg;
*h* — 8-para(metansulphonylamino)quinolin, 40–81 mg/kg; *i* — diphenylthiocarbazone (dithizon), 45–50 mg/kg

Figure 1. Complex salts of Diabetogenic Zincbinding Chelat Active Chemicals with Zn-ions and its diabetogenic doses

*Commentary and conclusions for Figure 1*. Information from Figure 1 show that in process of formation of chelates of zinc with derivatives of 8-oxyquinoline as 1:1 atom of zinc is fixed between the atoms of oxygen, nitrogen or sulfur located in position 8 and 1 or 2 only in molecule of derivatives whereas in complex zinc-dithizon atom of zinc is fixed between two atoms of sulfur too from two molecules of dithizon. More high stability of complex zinc-dithizon is determined by fixation of the atom of Zn between 2 atom of sulfur.

Stability of formed complexes 2:1 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 para-positions molecule of chelator, especially — in zones which contacted with part of molecule, reacted with ions of me- tal 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.

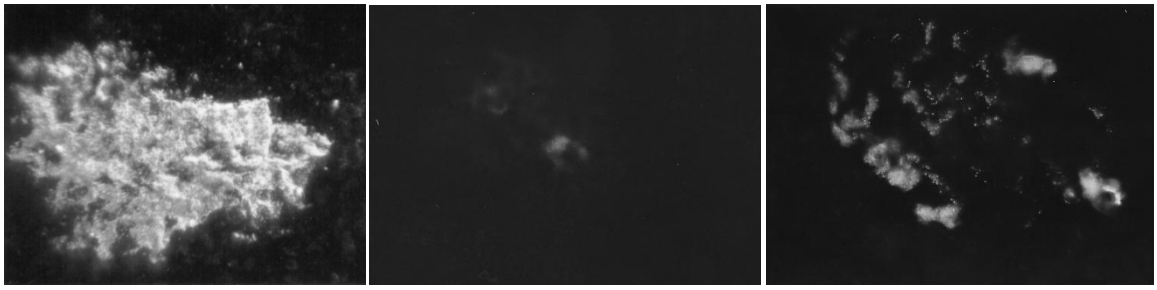
Stability of complexes 1:1 formed by derivatives of 8-oxyquinolin is determined by a: 1) great number of double coupling in molecule of chelator; 2) forming of quadragonal ring; 3) derivatives of 8-arensulphonylaminoquinolin formed chelat-complex by aid of atom of S. More high stability of the complex Zn–xanthurenic acid is determined in added by fixation of the atom of Zn between 2 atom of O [9].

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 1 h later injection. Shortening of period since starting of injection showed that 15 min. past injection in the contrary to 2 h cell's matrix was remained on 70–80 % of B-cell's surface but 30–40 % appeared as zone free of matrix or zone of complete destruction of ultrastructures of B-cells.

*Methods for prevention developing of diabetes caused by chelators. Protective effect of aminoacids gluthathione and cystein*

The aminoacids glutathione and cystein formed not toxic chelats with atoms of heavy metals due to sulfhydril 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 chelats 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. 2) 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. Thus, oxidized form of glutathione (GOF) have same structure but contrary to GRF not contain in structure of molecule of SH-radical. 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 2 3

*1* — Red granules of complex Zn-DZ in B-cells of rabbit; staining by DZ; darc microscopy; ×280;
*2* — 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; ×140;
*3* — Injection of GRF and 10 min later of DZ; prevention of formation of complex Zn-DZ as result of blocking of zinc by GRF; darc microscopy; ×280; histological sections and microphotographs by A.S. Shaybek and G.G. Meyramov

Figure 2

*Conclusions for Figure 2.* Results presented on Figure 2 demonstrate that: 1) GRF forming with zinc complex salt; 2) this complex is very stable and zinc from him can't be forced out by followed interaction with Dithizon.

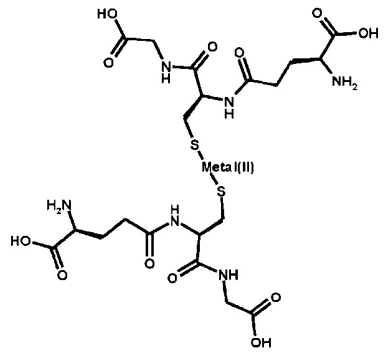



Figure 3. Disposition of zinc atom between 2 atoms of S of two SH-groups (by F.M. Rubino)

Analysis of structure of complex zinc-GRF demotstrate that as well as in complex zinc-ditizon zinc forms a complex with two molecules of GRF and also is fixed between two atoms of sulfur thanks to what its high durability is provided.

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-radical which is considered as the most dangerous among the free radicals. Decrease of amount of GSH increases susceptibility of animals to cytotoxins [17]. SH-radical possess chemical resistance against influence of peptidases. Atom of metal located between two atom of S of two molecules of Glutathione (Fig. 3).

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 $OH^-$. GRF as active reducer plays an important role in processes of a detoxification. Glutathione used for prevention and treatment of diabetic neuropathy in the streptozotocin-induced diabetic rat [18]. It is supposed that inactivation or change of SH-group of sulfhydril radicals in molecules of glutathione result complete disappearing of diabetogenic properties.

Injection of cystein, 1000 mg/kg prevent formation in B-cells of toxic chelat 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-oxyquinolin [19]. Aminoacid serin, which contained hydroxyl radical in molecule instead of sulfhydril 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 chelat 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).

*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 streptosotozin 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 formatuion in B-cells of not toxic chelat complexes as Zinc-NaDDC. Followed injection of DZ not accompanied by formation of toxic Zn-DZ complex in cytoplasm of B-cells and diabetes not developed. Thus, it was confirmed that presence of toxic chelat complexes of DZ and diabetogenic derivatives of 8-oxyquinolin 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.

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

Investigation of diabetogenic properties of dithizon and derivatives of 8-oxyquinolin have theoretical significance because these chemicals are not formed in human and really not delivered in human organism outside. In added peroral administration of its is not effective because they are not soluble and not absorbed in intestinum. Parenteral injection of diabetogenic chelators result developing of diabetes only. Meanwhile solutions of all these chelators are not stable and only injection of the fresh prepared solutions (ex tempore) result diabetogenic effect.

Among 18 diabetogenic derivatives of 8-oxyquinolin 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 [22, 23]. 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 [24–26]. High concentration of XA in the urine decrease by long time prolonged using of pyridoxine 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 diabetesgn animals as of solucose 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 contained in molecule as least 4 or 5 double chemical connections possess diabetogenic properties also in opposite to chelators 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 contains or 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 diabetogenic chelators.

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 protective activity of aminoacid glutathione reduced form (GRF) determined by its ability to prevent formation of toxic chelat complexes with DZC due to forming into B-cells of stable not diabetogenic chelat complexes with Zn-ions located in B-cells that protect Zinc from interaction with diabetogenic zincbinding chelators.

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## Химиялық кешенді қосылыстармен туындаған эксперименталды диабеттің дамуын аминқышқылдармен алдын алу әдістері туралы

Мақалада әдебиетке шолу жасау барысында соңғы онжылдықта адаммен байланысу мүмкіндігі біртіндеп артып, химиялық мырышбайланыстырушы заттар туындататын эксперименталды диабеттің дамуын алдын алу әдістері туралы деректер келтірілген. Олардың арасында негізгі назар бұрында маңыздылығына азырақ көніл бөлінген глютатионның аминқышқылды топтың алдын алу бейімділік қабілеті бар екендігі ескеріледі. Сондай-ақ глютатионның мырышқа 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. Сонымен қатар диабетогенді мырышбайланыстырушы заттар туындататын диабеттің дамуына жол бермейтін, молекула құрылымында сульфгидрильді топтардан тұратын тағы екі аминқышқылдың мүмкіндігі туралы деректер ұсынылды. Әдебиетке шолуда мырышқа қатысты кешенді қалыптастырушы қасиеттері бар кейбір дәрілік препараттар туралы ақпараттар келтірілген.

*Кілт сөздер:* В-жасушалар, диабетогенді мырышбайланыстырушы хелаттар, глютатион, инсулин, мырыш, глютатион тотықсыздандырылған күйі, глютатион тотыққан күйі, дитизон, 8-оксихинолин.

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## О методах предотвращения аминокислотами развития экспериментального диабета, вызванного химическими комплексообразующими соединениями

В обзоре приведены данные о методах предотвращения развития экспериментального диабета, вызываемого химическими цинксвязывающими веществами (ДЦВ), возможности контакта человека за последние десятилетия постепенно возрастают. Среди них главное внимание уделено ранее мало освещавшейся способности аминокислоты глютатиона предотвращать действие этой группы веществ. Показано, что высокая тропность глютатиона по отношению к цинку в значительной степени обусловлена наличием в структуре его молекулы SH-групп, через которые осуществляется недиабетогенное блокирование цинка, препятствующее связыванию его с диабетогенными хелаторами, что приводит к разрушению инсулинпродуцирующих В-клеток в течение 15–30 мин. Приведены также данные о спо-

собности двух других аминокислот, содержащих в структуре молекулы сульфгидрильные группы, предотвращать развитие диабета, вызываемого ДЦВ. В обзоре приведены сведения о некоторых лекарственных препаратах, обладающих комплексообразующими свойствами в отношении цинка.

*Ключевые слова:* В-клетки, диабетогенные цинксвязывающие хелаты, глютатион, инсулин, цинк, экспериментальный диабет, восстановленная форма глютатиона, окисленная форма глютатиона, дитизон, производные 8-оксихинолина.

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