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Prevention of developing experimental diabetes by reduced form of glutathione

Toxic properties of diabetogenic derivatives of 8-hydroxyquinoline (OX) and diphenylthiocarbazone (DC) on the insulin producing cells of the pancreas and the protective effect of glutathione on its toxic action have been investigated. The mechanism of action of OX derivatives is determined by their ability to form chelate salts of 1:1 composition with zinc-ions containing in B-cells via sulfur and nitrogen atoms at positions 8 and 1 and via the oxygen atoms in positions 8 and 2. Diphenylthiocarbazone forms chelates salts with zinc of 2:1 composition, where zinc is coupled to two molecules of dithizone via sulfur and nitrogen atoms. It is shown that the reduced form of glutathione (GR), containing SH-radical in the structure, has the preventing effect only, unlike the oxidized glutathione (GO) that doesn't contain the SH-radical. It is found that administration of GR to animals in the dose of 1000 mg/kg completely protects B-cells from destruction that is determined by formation of the zinc-GR complex that is not toxic for B-cells. It has been supposed that there are 2 possible types of complex of zinc with RFG: 1) that atom of zinc is fixed between atom of sulfur of the SH-radical and oxygen or nitrogen atom; 2) atom of zinc is fixed between two atoms of sulfur of two SH-radicals of two molecules of RFG that protect B-cells from formation of toxic complexes zinc-DC or zinc-OX.

Keywords: B-cells, reduced form of glutathione, oxidized form of glutathione, insulin, zinc, experimental diabetes.

Introduction

Diphenylthiocarbazon (DZ) and some diabetogenic derivatives of 8-hydroxyquinoline (OX) induce formation of toxic chelate complexes such as «Zn-DC» and «Zn-OX» in cytoplasm of B-cells that result in selective destruction of B-cells within 15–30 min and accompanied by developing of 1st type diabetes in animals [1]. Later it was reported the preventive injection of some amino acids such as cystein and reduced form of glutatione (GR) that contain sulfhydril groups (SH) in the structure of a molecule accompanied by protection of B-cells from destruction caused by DZ and OX that resulted in prevention of developing diabetes in majority of animals [2–5]. High durability of the Zn^{+2}-DC complex of the 2:1 composition (Fig. 2) is determined by space elongation of the DZ molecule and disposition of two phenolic rings on the ends of a molecule that does not prevent the atoms of sulfur and nitrogen located in the center of a molecule to approach zinc atom. Besides, zinc atom is located between atoms of nitrogen and sulfur, regarding to which affinity of zinc is very high and exceeds affinity to oxygen [6]. It was supposed that protective activity of cystein and histidine could be determined by the presence of sulfhydryl groups in a molecule because formation of chelate complexes with DZ and OX was processed by connection of Zn atoms with atom of S, H, O or N [6]. The purpose of investigation is to study the possible preventive effect of aminoacid GR on the model of isolated pancreatic islets.

Experimental Methods

Animals. 16 Rabbits, weight 2400–2850 g.

Group 1. Injection of DC, 48.6–51.2 mg/kg.

Group 2. Injection of RFG, 970–1010 mg/kg and 10 min later of DZ, 49.8–50.6 mg/kg; 4 animals from groups 1 and 2 were killed in 10 min after injection of DZ (1a; 2a) and 4 animals — in 9 days after injection (1b; 2b).

Group 3. Injection of GO, which doesn't contain SH groups in a molecule, 965 mg/kg. Animals were killed 15 min later. Staining zinc in frozen sections of pancreas was determined by 8-para(toluenesulphonylamino)quinoline (TSQ).

Group 4. Injection of GR, 1030 mg/kg. Animals were killed 15 min later. Staining zinc in frozen sections of pancreas was determined by TSQ.

Frosen sections of pancreas of animals 1a and 1b groups were investigated using dark microscopy. Blood glucose level was measured in animals of 1b, 2a and 2b groups before injection of DC and 1, 3, 6 and 9 days after injection. Aldehyde-fuchsine method [7–9] was used for analysis state of histostructure of pancreas tissue and dithizon method with formation of red granules of Zn^{+2}-DC complex that is visible using dark microscopy. Maximum of absorbance of Zn^{+2}-DC complex on spectrum of absorbance correspond for 530 nm [3]. TSQ, a high specific fluorescent reagent, was used for staining Zn-ions in B-cells. TSQ forms fluorescent green complexes with Zn^{+2}-ions that are visible using fluorescent microscopy [10–12].

Results

Group 1a. Administration of DZ accompanied by formation of a large amount of red granules of Zn^{+2}-DC complex in cytoplasm of B-cells (Fig. 1). Maximal concentration of granules located on the pole of B-cells contacted blood capillaries that correspond to concentration of deposited insulin.

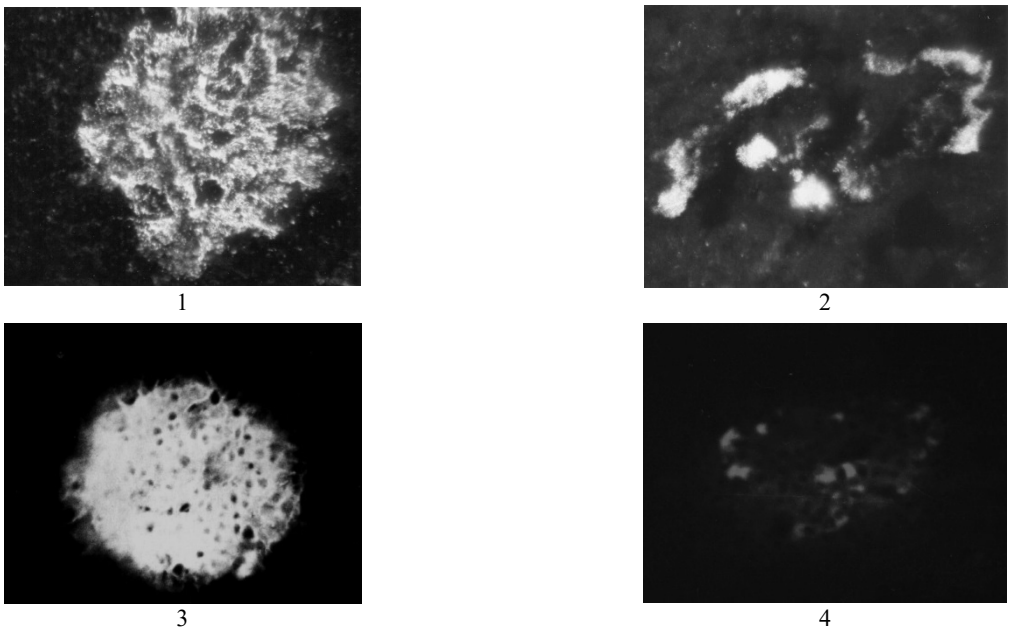
Group 1b. Experimental diabetes. Blood glucose concentration increased from 5.2 ± 0.3 mM to 12.6 mM at 6th day and 16.4 ± 1.7 mM at 9th day (Table). Histology: necrosis and destruction of 70–90 % of B-cells marked decreasing of insulin and zinc content in B-cells.

Group 2a. Preliminary injection of RFG resulted in almost complete prevention of formation of «Zn–DZ» complex in B-cells (Fig. 2).

Group 2b. Administration of RFG before dithizon accompanied by prevention of diabetes development in 3 animals from 4. In one rabbit (N3) blood glucose level increase till 9th day until 7.3. Histologic analysis showed decreasing of insulin content in cells without marked histological changes.

Group 3. Injection of GR: positive reaction for Zinc in B-cells with TSQ (Fig. 1.3) determined by absence of ability of OFG to bind zinc in B-cells; injection of DZ resulted in formation of complex zinc-DC in B-cells and development of diabetes.

Group 4. Injection of GR: negative reaction for Zinc in B-cells as result of binding by GR (Fig. 1.4)



1 2 3 4

1 — Pancreatic islet of intact rabbit. DZ, 46.8 mg/kg. Large amount of red granules of complex Zn-DZ in B-cells; Dark microscopy; ×280.
2 — Pancreatic islet. reduced Glutathione 1012 mg/kg + DZ Dithizon, 50.1 mg/kg. Almost complete absence of complex Zn-DZ in B-cells; Dark microscopy; ×280.
3 — Pancreatic islet. GO, 1015 mg/kg. Positive fluorescent reaction for Zn-ions in B-cells; ×140.
4 — Pancreatic islet. GR, 965 mg/kg. Negative fluorescent reaction for Zn-ions in B-cells; ×140.

Figure 1. Influence of RFG and OFG on amount of free zinc-ions in pancreatic B-cells

T a b l e

Blood glucose concentration after injection of Dithizon, reduced Glutathion (GR) + DZ and oxidized Glutation (GO)+DZ

Animals	Dose of GR and GO, mg/kg	Dose of DZ, mg/kg	Blood glucose concentration (mM)	
			before	9st day
DZ	–	47.5–52.0	5.34±0.32*	19.8 ±1.72*
GR+DZ	1005–1018	49.3–51.9	5.30±0.55	5.81±0.40
GO+DZ	955–1015	46.8–50.2	5.48±0.56*	17.25±2.60*

Note. * — $p \leq 0.005$.

Discussion

Results obtained showed that administration of RFG resulted in binding almost all amount of Zn-ions in B-cells reversibly as least for 24 hours. Injection of DC after RFG was not accompanied by forming chelate complexes Zn-DC in B-cells that resulted in prevention of damage and death of majority of B-cells and prevention of developing diabetes in 3 animals from 4. It is known that aminoacids cystein and L-hystidine possess the same property and their injection protects B-cells from destruction caused by DC and developing diabetes in animals [6, 13]. Howerer, administration of OFG that doesn't contain SH-radicals in the structure doesn't protect B-cells from formation of Zn-DC complex and from destruction and developing diabetes [13]. Binding of Zn-ions of B-cells by glutathione was apparently confirmed by existence of negative reaction for Zn during 24 hours. After that the complex gradually dissociated up and 48–72 hours later DC was able to form toxic complex in B-cells that accompanied by developing experimental diabetes in animals.

It is known that in the process of formation of the Zn^{+2}-complex with DC or OX zinc atom is fixed between S or O atoms in position 8, and N or O atoms — in positions 1 or 2 (Fig. 2) [14]. OX contains active OH^- radical in the 8 position of quinoline ring or other radicals that contain S, N or O atoms (Fig. 2).

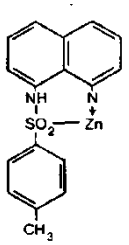
A. Albert [14] showed that 8-hydroxyquinoline, which is usually non-toxic one, is very toxic for cells in the presence of metals, especially in the presence of Zn-ions. It was showed that the possibility was determined by ability of OX to form the chelate metal-complexes, which are toxic for B-cells [14] as complexes formed in B-cells by other chelate active substances such as DC. Studying toxicity of OX for B-cells K. Okamoto [1] reported that injection of it to animals was accompanied by destruction of pancreatic B-cells and developing experimental diabetes. Later it was showed that injection of 18 derivatives of OX was accompanied by destruction of B-cells within 15–30 min that resulted in developing heavy diabetes in animals. It was noted that all those chemicals had OH^- group or any other radical containing S atom or O or N atoms in position 8 of quinoline ring. It was showed that OX possessed high affinity for zinc and formed chelate salts with zinc via radical in position 8 (Fig. 2).

Six isomers of OX that do not contain active groups in position 8 are not able to form chelate complexes with Zn-ions and do not induce experimental diabetes. Experimental diabetes is induced by derivatives such as 8-para-(toluenesulphinylamino)quinoline (8PTSQ), 8-para-(benzenesulphonylamino) quinoline (8PBSQ), 8-para-(methanesulphonylamino)quinoline (8PMSQ), 5-para-(acetaminophenylazo)-8-oxyquinoline (5A8OX), 8-hydroxyquinaldin, 5-amino-8-hydroxyquinoline and others (Fig. 2). It was demonstrated that injection of those derivatives resulted in selective necrosis of B-cells. Injection of those chemicals in doses of 30–100 mg/kg resulted in developing heavy diabetes with marked degenerative changes in islets within a few days [1, 3, 4, 11].

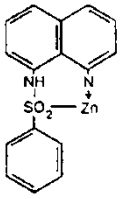
It is known that the most stable complexes are formed when atom of Zn is fixed between S and O atoms in position 8 and between N and O atoms in position 1 or 2. It was showed that only derivatives of 8-hydroxyquinoline, which contained the hydroxyl or another radical with S, N or O atoms in position 8 of quinoline ring, possessed diabetogenic properties [14]. It is known that extraction of these radicals from position 8 is accompanied by complete disappearing of diabetogenic properties of chelators [15]. Formation of chelates by O and N atoms of chelator usually results in forming pentagonal or hexagonal rings [1, 14] (Fig. 2). Pentagonal rings are more stable. Quadrangular complexes with S atom are the most stable ones. It is known that OX derivatives, which form quadragonal complexes with atom of S, are often stable ones. Unshared pair of electrons is displaced from N donor-atom in position 1 to Zn atom.

On the basis of data obtained by A. Albert it is supposed that toxic effect of OX was determined by its ability to bind and eliminate metal ions from B-cells. But later this hypothesis was not confirmed. It was showed that the prolonged elimination of Zn-ions from B-cells did not affect on the state of histostructure and

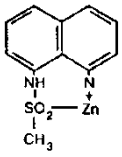
function of B-cells. Finally, S. Rubbo and A. Albert established that toxic effect of OX was determined by its ability to form toxic complexes with metals in cells [16] that many times was confirmed later. It was showed that presence of chelate in cytoplasm of B-cells for a short time was accompanied by alteration of cells. In experiments with azaoxyquinoline (azaoxyn) it was demonstrated that the most toxic were chelates of 1:1 composition with logarifm of stability constant that was equal to 7.6 and higher, up to 9.4. Meanwhile, toxicity of chelates of other isomers of azaoxyn with stability constant 5.8–6.7 was clearly less [5, 14]. It was showed that very toxic chelates of derivatives of 8-hydroxyquinoline with Zn-ions had higher logarithm of stability constant 8.5. G. Weitzel and coll. showed that 1:1 complex contained 1 molecule of 8-hydroxyquinoline and 1 atom of Zn ion was the most toxic for cells [17].



8-para-(toluenesulphonylamino)-quinoline, 30–50 mg/kg



8-para-(benzenesulphonylamino)-quinoline, 30–100 mg/kg



8-para-(methanesulphonylamino)-quinoline, 40–81 mg/kg

Figure 2. Complex salts of diabetogenic zinc-binding chelate active chemicals with Zn-ions and its diabetogenic doses

Stability of 2:1 complexes depends not only on affinity of chelator for metal but on two other properties of chelator and metal: 1) presence of additional radicals in para-positions of chelator molecule, especially in zones contacted with part of a molecule reacting with metal ions with formation of the steric effect. As a result, two molecules of chelator are not able to approach to put an atom of metal in a stable ring; 2) diameter of atom; if a metal atom has a small diameter, ring may be not formed. Zn atom has radius 0.74 nm and it is between berillium (0.31 nm) and rubidium (1.49 nm). A high stability of Zn-DC complex is determined by elongated form of the DC molecule and by location of two phenol rings on two ends of a molecule. That is why N and S atoms are easy to approach to Zn atom. Moreover, Zn atom is fixed between N and S atoms. Meanwhile, it is known that affinity of Zn for N and S atoms is higher comparatively with affinity of Zn for O. In addition, complex formed by two molecule of DZ each of two has a great number of double bonds [1, 5, 14].

Stability of 1:1 complexes formed by derivatives of 8-hydroxyquinoline is determined by a great number of double bonds in a molecule of chelator as well as by forming of quadragonal ring. Derivatives of 8-arenesulphonylaminoquinoline form chelate-complex via S atom. Higher stability of the complex Zn-xanthurenic acid is determined by fixation of the Zn atom between two O atoms.

Isomers of 8-hydroxyqunolines, which do not contain such radicals or atoms in this position (8), or if these radicals are extracted from a molecule, are not capable for forming complex salts with zinc and do not possess diabetogenic properties completely. It is necessary to return the active radicals in position 8 to restore diabetogenic activity of substance [15]. Formation of the chelate complex by O and N atoms is accompanied by forming pentagonal or hexagonal rings [14].

SH groups contain sulfur atom. Meanwhile, as it is described above, it is known that sulfur atom participates in formation of the chelate complexes with Zn as well as N, O and C atoms. It is known that in process of formation of the Zn^{+2}-complexes with DC and OX zinc atom is fixed between S or O atoms in position 8, and N or O atoms — in positions 1 or 2 (Fig. 2) [14].

On the basis of the results obtained we suppose that negative fluorescent reaction for Zn in B-cells after administration of reduced form of glutathione was determined by binding of Zn-ions via atom of sulfur of the SH-group and by disposition of zinc atom between atom of sulfur and, probably, atom of oxygen (Fig. 3) or nitrogen or, more probably, is fixed between two atoms of sulfur from the two molecules of reduced glutathione [18].

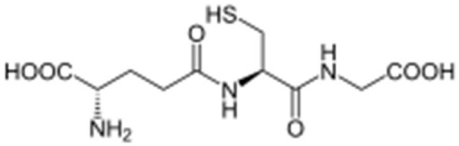


Figure 3. Reduced Glutathione

Conclusions

Reduced form of glutathione, which contains sulfhydryl radical in the structure in the dose of 1000 mg/kg, prevents formation of zinc complexes with diabetogenic zinc-binding chelators in B-cells, protecting B-cells from destruction as well as preventing from development of diabetes in animals. Oxidized form of glutathione, which doesn't contain sulfhydryl radical in the structure in the dose of 1000 mg/kg does not protect B-cells from formation of complexes with DC and does not protect B-cells from destruction and from developing diabetes in animals.

Administration of reduced form of glutathione to animals resulted in blocking of Zn-ions in B-cells that protects from interaction of metal with DC. We suppose that preventive effect after administration of reduced form of glutathione was determined by binding Zn-ions via atom of sulfur of the sulfhydryl radical and followed by disposition of zinc atom between atom of sulfur and atom of oxygen or nitrogen.

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Эксперименттi диабеттiң дамуын глютатион аминқышқылы көмегiмен алдын алу

Авторлар оксихинолиннің және дифенилтиокарбазонның диабетогенді туындыларының зақымдаушы қасиеттерінің ұйқы безінің инсулин өндіруші жасушаларына және глютатион аминқышқылдарының олардың уытты әсерін алдын алуға қатысты әсерін зерттеген. Оксихинолин (ОХ) туындыларының әсер ету механизмінде олардың құрамында мырыш бар жасушаларда, онымен бірге ішкі кешендік тұздар құрамы 1:1, 8 және 1-қалыптардағы күкірт және азот атомдары арқылы және 8 және 2-қалыптардағы оттегі атомдары арқылы қалыптастыру қабілеті бар. Дифенилтиокарбазон (DC) құрамында 2:1 мырыш бар хелат түзеді, мұнда мырыш дитизонның екі атомымен күкірт және азот атомдары арқылы қосылады. Глютатионның тотыққан формасынан айырмашылығы, алдын алу әсеріне құрылымында SH-радикалы бар глютатионның тотықсызданған формасы ие екендігі көрсетілген. Жануарларға тотықсыздандырылған глютатионды 1000 мг/кг дозада бірретті енгізу В-жасушаларының бұзылуына және жануарларда диабеттің дамуына әкелетін уытты кешендерді қалыптастырумен В-жасушалардың мырышты байланыстыруға толық кедергі келтіретіні анықталды. Тотықсызданған глютатионның аралшықтардағы мырышпен өзара әрекеттесуінің химизмін зерттеу, оны енгізу жасушаларда мырышты толық бұғаттылуымен қатар жүретінін көрсетті, зерттеу нәтижесінде ол жоғары арнайы гистохимиялық әдістердің көмегімен гистохимиялық жолмен айқындалмайды. Авторлар тотықсызданған глютатионның алдын алу қабілеті оның аралшықтардағы мырышты байланыстыру қабілетіне байланысты деп санайды: 1) мырыш атомы бұл ретте SH-радикал күкірт атомы мен оттегі немесе азот атомы арасында тіркеледі, бір жағынан, күкірт атомы және оттегі атомы, екінші жағынан, 2) азот арқылы аралшық мырышты байланыстыратын ОХ немесе DC туындысы енгізілген жағдайларда да глютатион молекуласында бар деп пайымдайды.

Кілт сөздер: В-жасушалары, глютатионның қысқартылған түрі, глютатионның тотығу формасы, инсулин, мырыш, тәжірибелік диапазон.

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О предотвращении развития экспериментального диабета с помощью аминокислоты глютатиона

Были исследованы повреждающие свойства диабетогенных производных оксихинолина (ОХ) и дифенилтиокарбазона (DC) на инсулинпродуцирующие клетки поджелудочной железы и предупреждающее влияние аминокислоты глютатиона в отношении их токсического действия. Механизм действия производных ОХ имеет способность формировать в клетках, содержащих цинк, внутрикомплексные соли с ним состава 1:1 через атомы серы и азота в положениях 8 и 1 и через атомы кислорода в положениях 8 и 2. Дифенилтиокарбазон формирует хелаты с цинком состава 2:1, где цинк соединяется с двумя атомами дитизона через атомы серы и азота. Показано, что предотвращающим действием обладает восстановленная форма глютатиона, содержащая в своей структуре SH-радикал, в отличие от окисленной формы глютатиона, не содержащей его и не обладающей предотвращающим эффектом. Установлено, что однократное введение восстановленного глютатиона животным в дозе около 1000 мг/кг полностью препятствует связыванию цинка В-клеток с формированием токсических комплексов, вызывающих разрушение В-клеток в результате последующего введения ОХ и DC и развитие диабета у животных. Исследование химизма взаимодействия восстановленного глютатиона с островковым цинком показало, что введение его сопровождается полным связыванием цинка в В-клетках, в результате чего он не выявляется гистохимически с помощью высокоспецифичных гистохимических методов. Предупреждающая способность восстановленного глютатиона обусловлена его способностью связывать островковый цинк двумя путями: 1) атом цинка при этом может фиксироваться между атомом серы SH-радикала и атомом кислорода или азота, содержащимися в молекуле глютатиона, как и в случаях введения производных ОХ или дифенилтиокарбазона, связывающих островковый цинк через атом серы, с одной стороны, и атомом кислорода, либо азота, с другой стороны; 2) атом цинка может фиксироваться между двумя атомами серы от двух SH-групп, входящих в состав двух молекул восстановленного глютатиона.

Ключевые слова: В-клетки, восстановленная форма глютатиона, окисленная форма глютатиона, инсулин, цинк, экспериментальный диабет.

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