значительное количество ацетальдегида сами и поэтому этот феномен можно назвать избирательностью или тропностью. В связи с цитированными данными и по полученным результатам, можно предположить, что способствовать прикреплению большего количества клеток грибов рода *Candida* к поверхности буккальных эпителиоцитову курильщиков сигарет, конечно, будет наличие этой вредной привычки.

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

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Известно, что содержащийся в β-клетках поджелудочной железы цинк принимает важное участие в образовании его депонированной формы хранения в клетке, благодаря чему не весь синтезированный клеткой гормон, а только определенные его количества по мере необходи- мости поступают в кровь, регулируя обмен углеводов и обеспечивая поддержание уровня глю- козы крови на постоянном уровне. Известно также, что существуют цинксвязывающие диабе- тогенные вещества (ДЦС), 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, отде- льные представители которых являются компонентами 12 лекарственных препаратов (в 1970 г. их было 2). Известно также, предварительное введение аминокислоты Цистеин полно- стью предотвращает развитие диабета, вызываемого ДЦС. Предположительно это обосновы- вается ее способностью в использованных дозах на 24-36 час. блокировать цинк, не давая ему возможности взаимодействовать с ДЦС. Авторами с помощью чувствительных и строго спе- цифичных методов установлено, что, действительно, цистеин блокирует островковый цинк, предотвращая его взаимодействие в ДЦС. 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 ами- ногруппы молекулы Цистеина, как это имеет место и при взаимодействии цинка с ДЦС, где хелаты с цинком формируются только в результате фиксации их между этими атомами.

Ключевые слова: В-клетки, цинк, цистеин, поджелудочная железа

Introduction. Pancreatic islets of many mammals as rabbits, dogs, cats, pigs, mice, horses, hamsters and of human contains a large amount of ions of zinc [1-3] 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 increases solubility of proinsulin. It is known a group of diabetogenic chemicals [1-3, 6-9] 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.

Aim of work: to investigate possibnsulinle interaction of zinc in pancreatic B-cells with Cystein

Key words: pancreas, pancreatic islets, B-cells, histochemical methods, dithizon, Cys- tein, zinc, insulin, histotopography, quantitative analysis.

Abbreviations: DZS –diabetogenic zinc binding chemicals TSH-Para(toluenesulfonyl-amino)quinoline; DZ- Dithizon

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

For to induce experimental diabetes two DZS were used. Diphenylthiocarbazon (DZ) and Para(toluenesulfonilamino)quinoline (TSH) possess two important properties for this purpose: 1) to form with zinc in β-cells chelat complexes highly specific for zinc; 2) complexes with TSH have bright green fluorescence [1,2,7-9] 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 8TSH 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 absorbance 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 TSH: 25 mg. powder 8TSH (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. TSH formed fluorescent complexes with zinc and cadmium. But cadmium is absent in pancreatic β-cells. That is why TSH for β-cells is high specific for staining of zinc ions [12].The complex Zn^{+2}-TSH 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 [12-14].

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 tiss ueby 8TSHor after intravenous injection of 8TSH. 0,4% aceton solution of 8TSH 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}-8TSH 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 (8TSH) and of density of staining (Dithizon) of β-cells and content of zinc.

Calculation of parameter K for a 8TSH-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). Calcu- lation 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 TSH reaction: a large amount of zinc in β-cells of intact animals - the intensive bright green luminescence of a complex Zn^{+2}-TSH (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 8TSH 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 radi cals 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 chelat-complex 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 dura- bility 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 mo- lecule 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. Weitzel G. and coll.[18] confirmed that the complex 1:1 contains 1 molecule of derivatives of oxyquinolin and 1 atom of zinc is most toxic for cells.

High durability of the Zn^{+2}-Dithizon complex 2:1 (Figure 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.

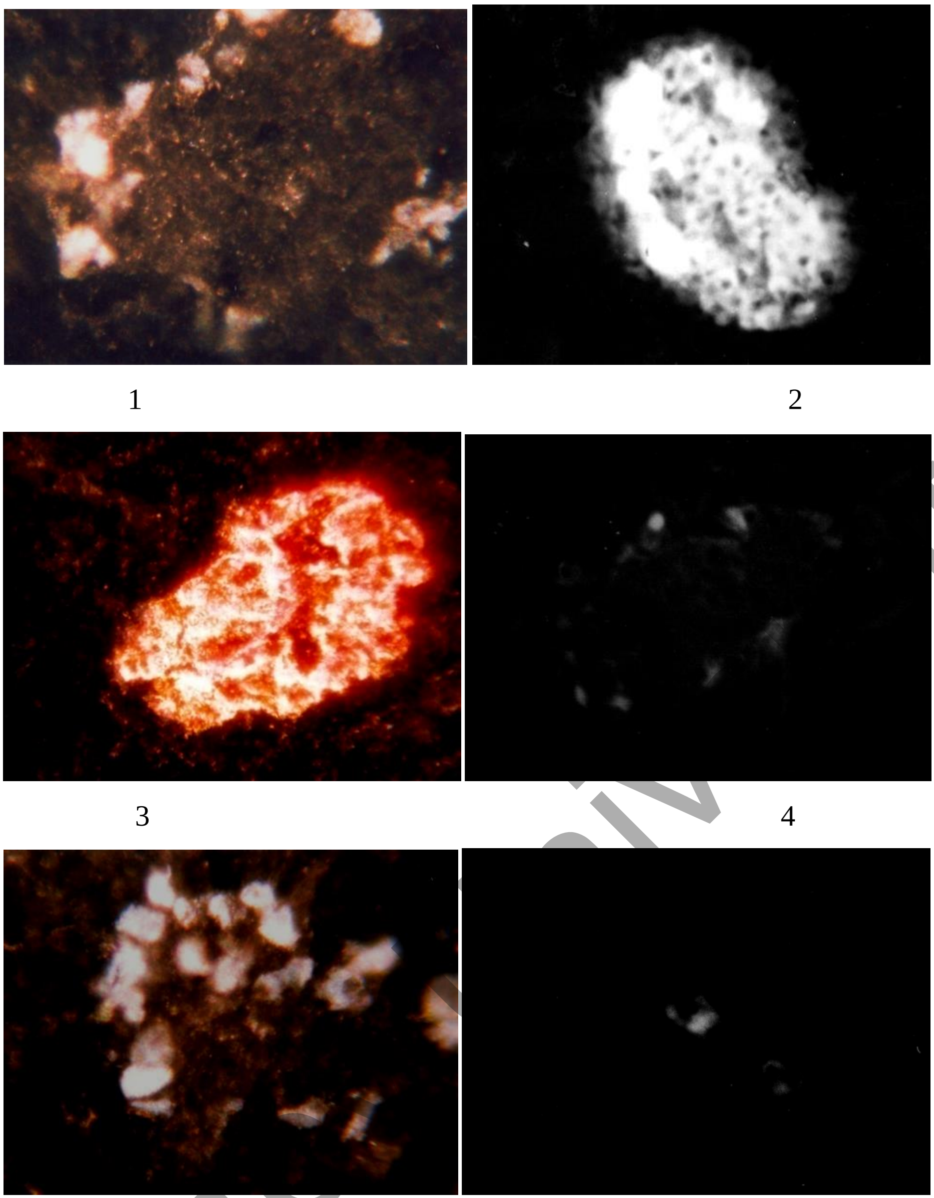


Figure 1. Interaction of DZ and GSH with zinc ions in pancreatic B-cells

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. 8TSH 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; darc microscopy;x280; 1.4-Injection of DZ , 49,3 mg/kg; negative reaction for Zn^{+2}-ions in B-cells with 8TSH: zinc in B-cells is connected with DZ; fluorescent microscopy;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 TSH as result of binding of zinc with Cystein; fluorescent microscopy; x140

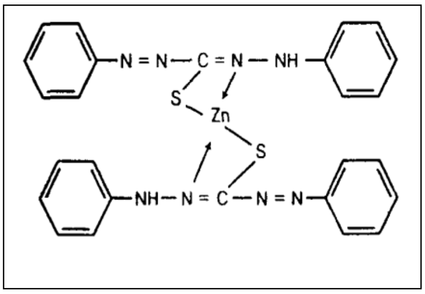
Table 1.

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

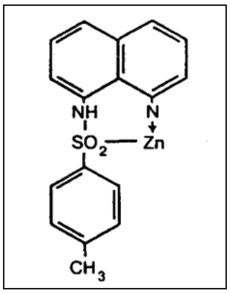
Group №	Experimental conditions	Insulin content in pancreatic β-cells (r.e.)	
		8-TSH reaction (zinc) (IF1/IF2)	Dithizon reaction (zinc) (AF1/AF2)
1	Intact rabbits	2,04±0,08 (n=22)	1,02±0,04 (n=20)
2	DZ	1,02±0,04 (n=16)	1,95±0,07 (n=18)
3	GRF+DZ	1,02±0,04 (n=20)	1,03±0,03* (n=23)
4	GOF+DZ	1,05±0,04 (n=21)	1,92±0,06* (n=18)

* p<0,001; n- number of measurements

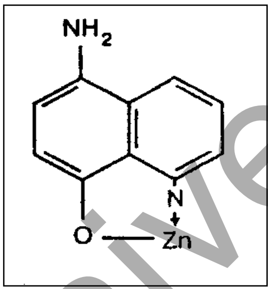
Fig.2. Structure of zinc complexes with DZ, Oxyquinoline and Cystein



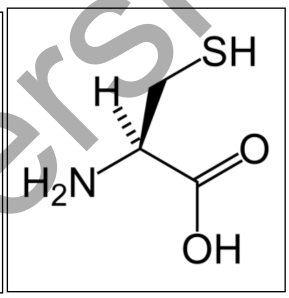
Dithizon diabetes



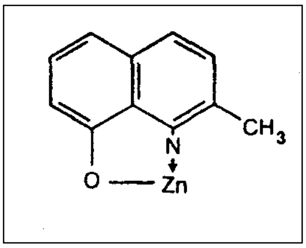
TSH diabetes



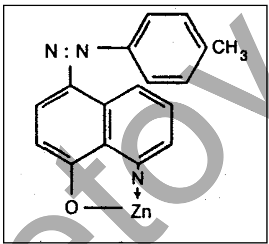
5-amino-8-oxyquinolin d iabetes



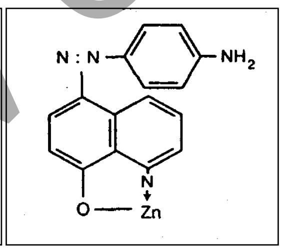
Cystein-Zn (located betweeb atom of O and SH radical not diabetes



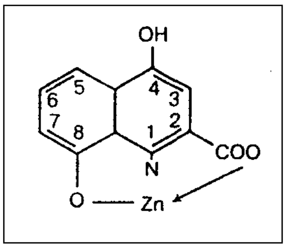
Oxyquinaldine



5-para (toluene)-8-oxyquinolin



5-para (aminophenylaso)- -8-oxyquinolin



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

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 toxi- city for B-cells formed with Zn have a high rate of logarithm of a constant of stability, equal 8,5. Weitzel G. and coll.[18] confirmed that the complex of structure 1:1 cont- ains 1 molecule of 8-oxyquinolin and 1 atom of zinc is most toxic for cells.

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,Mexaformand 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.

Conclusions:

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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ААҚ «АТЫРАУ» ШИПАЖАЙЫНЫҢ ЖЕРГІЛІКТІ ХАЛЫҚТЫҢ ДЕНСАУЛЫҒЫН САҚТАУДАҒЫ МАҢЫЗЫ

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Атырау шипажайы –денсаулықты қалпына келтіру, созылмалы ауруларды емдеу және алдын алу шараларына бағытталған. Қызмет сапасы шипажайдың білікті мамандар құрамына және заманауи емдеу технологияларын қолдануға байланысты.

Кілт сөздер: шипажай,емдік балшық,минералды ванна, ауруларды алдын алу, тұзды көл.

The Atyrau sanatorium is aimed at rehabilitation, treatment and prevention of chronic diseases. The quality of service depends on the composition of qualified specialists of the sanatorium and the use of modern treatment technologies.