Short Article

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Diabetogenic Zinc Binding B-Cytotoxic Chemicals: Mechanisms of Action and Methods for Prevention of Diabetes

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Abstract

Mechanisms of diabetogenic action of diabetogenic zincbinding chemicals (DZBC) as Dithizon and derivatives of 8-oxyquinolin and methods of prevention of diabetes caused by their were investigated. It was established that: a) injection of diabetogenic doses of DZBC as 30-50 mg/kg result forming in bytoplasm of B-cells of chelat complexes Zn-DZBC within a few minutes; b) by electron microscopy it was showed that presence of complex in B-cells within 15-20 min result destruction and death of majority B-cells and developing of 1 type diabetes in animals; c) destruction of B-cells started by destroying of B-granules concentrated deposited form of insulin as Zn-insulin; d) prevention of formation of comlex in B-cells by 2 ways (complete elimination of Zn-ions from B-cells by Glibenclamide or binding of Zn-ions by not diabetogenic chelators as Na salt of Diethyl-dithiocarbamic acid, by Cystein and recovered form of Glutathion completely protect B-cells of formation of complex and of developing of diabetes in 85-95% of animals for period of binding of Zn-ions (12-24 h); e) Xanthurenic Acid formed in animals and human as result of disturbances of tryptophan metabolism possess same mechanism of action as other DZBC but diabetes developed more slowly because XA is synthesised in organism more slowly that is why not possible to destroy majority of B-cells as in result of injection of diabetogenic doses of other DZBC; f) they are only one real way for prevention action of XA- partial or mo complete inhibition of endogene synthesis of XA by administration of Pyridoxine (P) within long time due to ability of P to restore amount of Pyridoxal-5-Phosphate which protect endogene synthesis of XA; two other ways (elimination of Zn-ions and not diabetogenic binding of its) not possible to use for protect developing of diabetes or to reduce its symptoms.

Introduction

More than 80 years ago A Scott and D Fischer were separated insulin from the native pancreas as insulin-Zn^{+2} complex and supposed that the presence of Zn^{+2}-ions determined physiological activity of insulin. Interest to this problem was increased after reporting by these authors that in pancreas of diabetic patients total amount of Zn is not more than 50% in compared with non-diabetic men.

The amount of Zn^{+2} is evidently decreased in experimental diabetes induced by any causes. Zn^{+2} is able to accumulate in pancreas tissue. By aid of electron histochemical microscopy it was confirmed that in B-cells Zn^{+2}-ions are located in B-granules contains deposited form of insulin.

1. 1964-1967. Analysis of problem; mastering of research methods.

2. 1967-1977. Investigation of mechanisms of Diabetogenic Zinc binding [1] B-cytotoxic Chemicals, DZBC [2-5] (derivatives of 8-oxyquinolin and Dithizon) and methods for prevention of diabetes caused by their.

Methods

Animals: rabbits and rats. Histological and Histochemical methods for staining of insulin and of Zn^{+2}-ions were used: Methods: aldehyde-fucshine, fluorescent pseudoisocyanine method, immunohistochemical method, Victoria-4R, Dithizon histochemical method and high specific fluorescent method for staining of Zn^{+2}-ions; transmission electron microscopy; method of isolation of pancreatic islets by using of Collagenase was used for to investigate direct action of DZBC on B-cells on model of tissue culture.

Results

a)DZBC formed in B-cells toxic chelat complexes with Zn^{+2}-ions that result destruction of cell matrix and of B-granules on 30-40% of B-cells surface within 15-30 min. and on 85-95% of surface 2 h past injection of diabetogenic doses of DZBC and developing of 1 type of diabetes; 1.5-2 h later chemical complex disintegrates in B-cells; analogical results were obtained using tissue culture model of experience; b) elimination of Zn^{+2}-ions from B-cells protect B-cells of destruction and of developing of experi-mental diabetes in 95-100% animals; c)preventive not diabetogenic binding of Zn

$^{+2}$-ions in B-cells by not diabetogenic ligands as aminoacids (Figures 1a-1f) recovered Glutathion, Cystein and salts of Dithiocar-bamic acid, protect B-cells of destruction and of developing of diabetes in all animals for 12-24 h.

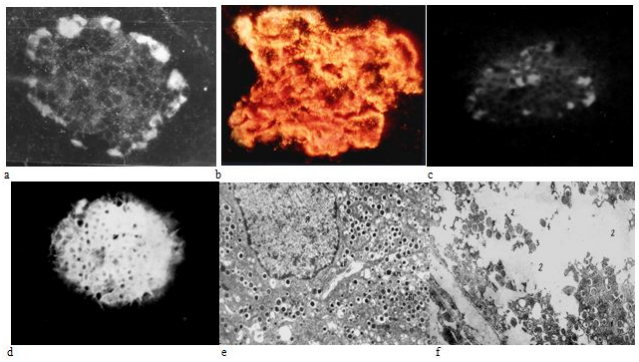

Figure 1: a) Frozen section of intact pancreas of Rabbit without staining. b) Past injection of Dithizon, 50, 2 mg/kg; red granules- complex "Dithizon-Zn" in B-cells. c) Frozen section of intact pancreas without staining; intensive fluorescence of complex "8-p(toluene-sulphonylamino)quinoline-Zn" in B-cells. e) Transmission electron microscopy of B-cell of intact Rabbit. f) Transmission melectron microscopy of B-cell 2 h past injection of Dithizon: destruction of B-cell's matrix.

Oxidized Glutathion not containing SH-group not protect B-cells interaction of Zn^{+2}-ions with DZBC and as result of destruction as of developing of diabetes.

3. 1980-2018. Investigation of diabetogenic activity of the one of 16 derivatives of 8-oxyquinolin as Xanthurenic Acid (XA) unlike all other DZBC is synthesized in the organism of human as result of disturbances of Tryptophan [6] metabolism: a)mechanisms of diabetogenic action of XA; b) search of methods for suppression of synthesis of XA in animals. Results: a) XA formed as other DZBC in B-cells of toxic complex with Zn^{+2} but accumulates in organism [7] slowly and diabetes developed on clinical aspect as 2 type; aggravation of diabetes caused by XA (Figure 2) is determined by destruction of capillaries wall, contacted B-cells contains chelate complexes with Zn^{+2} in islets that accompanied by [8,9] disturbances of blood microcirculation; b) treatment of rats with diabetes induced by XA by Pyridoxine, 150 mg/kg per 2 days within 3-3.5 months result decreasing of xanthurenuria 0.366 ± 0.14 mg/100 ml until 0.118 ± 0.008 mg/100 ml (intact control: 0.035 ± 0.005) by decreasing of blood glucose level until 8.1 ± 0.5 mM from 12.6 ± 0.6 mM ($p<0.005$) and by weakening symptoms of diabetes in animals.

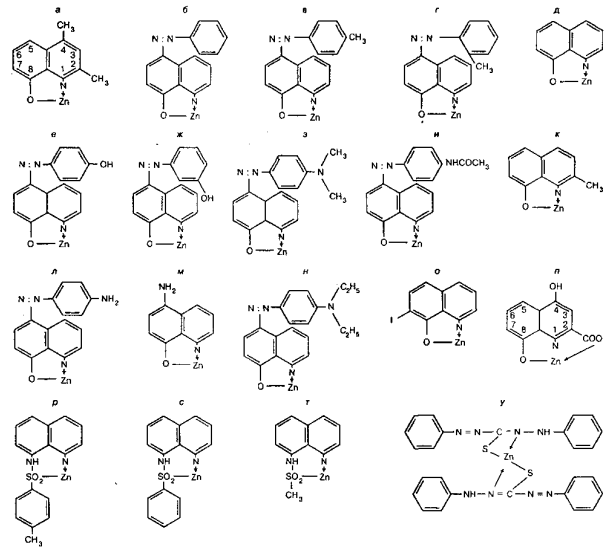

Figure 2: Complex salts of Diabetogenic Zincbinding Chelat Active Chemicals with Zn-ions and its diabetogenic doses: а) 2,4-dimethyl-8-oxyquinolin, 35 mg/kg.б) 5-phenylaso-8-oxyquinolin, 20 mg/kg. в) 5-para (toluene)-8-oxyquinolin, 20 mg/kg. г) 5-orto- (toluene)-8-oxyquinolin, 40 mg/kg. д) 8-oxyquinolin, 50-60 mg/kg. е) 5-para (diethylaminophenylaso)-8-oxyquinolin, 20 mg/kg. ж) 5-meta (hydroxyphenylaso)-8-oxyquinolin, 30 mg/kg. з) 5 para (dimethylaminophenylaso)-8-oxyquinolin, 45 mg/kg. и) 5-para(acetylami- nophenylaso)-8-oxyquinolin, 50 mg/kg. к) 8-oxyquinaldin, 10 mg/kg. л) 5-para (aminophenylaso)-8-oxyquinolin, 10 mg/kg. м) 5-amino-8-oxyquinolin, 30 mg/kg. н) 5-para (diethylaminophenyla- so)-8-oxyquinolin, 40 mg/kg. о) 9-oxy-7-jodoquinolin, 50-60 mg/kg. п) 4,8 – dihydroxyquinolin-2 carboxylic acid (xantu- renic acid). р) 8-para (toluenesulphonylamino)quinolin, 30-50 mg/kg. с) 8-para (benzolsulphonylamino)quinolin, 30-100 mg/kg. т) 8-para (metansulphonylamino)quinolin, 40-81 mg/kg. у) diphenylthiocarbazone (dithizon), 45-50 mg/kg.

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