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Diabetogenic Metabolits of Tryptophan

The analysis of results investigations of mechanisms of diabetogenic activity of metabolits of abnormal tryptophan metabolism as Xanthurenic acid (XA) are presented in review. Among more than 30 diabetogenic chemicals widely known today XA only is formed in animals and elderly human as result of disturbances of tryptophan metabolism. The influence of XA on histostructure of pancreatic islets and on insulin content in B-cells as mechanisms of diabetogenic action and of its prevention are investigated by authors. It was showed that Xanthurenic acid induced diabetes determined by: direct damage of B-cells by Xanthurenic acid accompanied by marked histological changes in islets as destruction and necrosis of B-cells, marked decreasing of insulin content in cytoplasm of cells; by forming of complex XA-insulin that result overstrain of B-cells; by alteration of islet's capillaries and of blood microcirsulation.

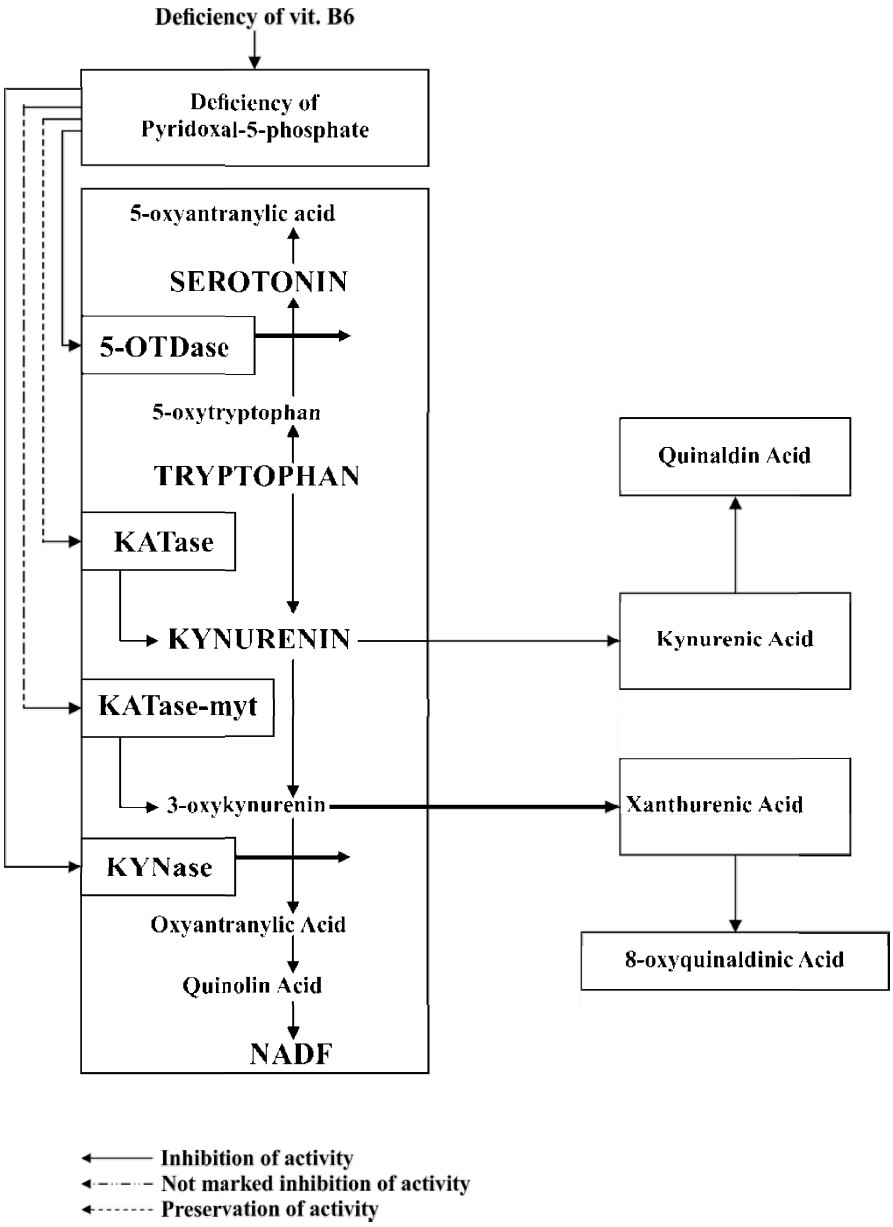
Key words: B-cells, Xanthurenic acid, experimental diabetes, tryptophan, pancreas.

In 1935 Musajo L. and coll. reported about synthesis of Xanthurenic acid (XA). This chemical was separated from urine of experimental animals and identified as 4,8-digidroxyquinolin-2-xarboxylic acid, a derivative of 8-oxyquinoline [1]. Formula: $C_{10}H_7NO_4$.

Accumulation in organism of large amount of fatty acids and tryptophan in the deficiency of vit. B6 (pyridoxine) result intensive synthesis of XA in tissue. It was followed by developing in animal symptoms of diabetes [2–8].

Xanthurenic acid is a product of disturbances of Tryptophan metabolism, in routine conditions is metabolised on serotonin and kinurenine ways (Fig. 1) which at the same time come to the end with forming of a 5-oxyindol-acetic acid and NADF [9, 10]. The deficiency of pyridoxal-5-phosphat (P-5-F) result inhibition of 5-oxytryptophan decarboxylase and of kinureninase that accompanied by inhibition of metabolisation on both paths. As result — 4 substances are formed: Xanthurenic acid and 8 oxyquinaldine — from 3-oxyquinurenine and kynurenic and oxyquinurenic acids — from kynurenine [10–12]. Main enzymes for synthesis of Xanthurenic acid are kynureninaminotransferase and oxykynurenine-tryptophandecarboxylase, a coenzymes of P-5-P [10, 13]. XA is formed from 3-oxykynurenine. Under influence of a kynureninaminotransferase from 3-oxykynurenine Xanthurenic acid is formed. In the deficiency of P-5-P synthesis of serotonin is decrease and synthesis of XA and of kynurenine acid is increased [2, 14]. However there is, apparently, a contradiction: why deficiency of P-5-P inhibit synthesis of serotonin and stimulate synthesis of XA? On the one hand this results based on fact that the pyridoxal enzymes of tryptophan metabolism differently react for deficiency of P-5-P: if activity of a kynureninase decrease by 83 %, then of kynureninaminotransferase — decrease for only 42 % [13, 15]. On the other hand, studying of localization of enzymes in cells of liver and kidneys it was established that the kynureninaminotransferase is both in mitochondria and in soluble part of cells whereas a kynureninase — only in a soluble part of cells. In the deficiency of P-5-P in organism the content of these two enzymes in soluble part of cells significantly decrease, and of mitochondrial kynureninaminotransferase remains at the previous level [16]. Increasing of excretion with urine of xanthurenic acid is explained by it. For the first time the high amount of Xanthurenic acid were found in the urine of the white rats who were contained on diet enriched with tryptophan and in deficiency of vit. B6.

Addition of Pyridoxine accompanied by disappearance of Xanthurenic acid from urine [9, 12, 17]. However, marked avitaminosis of B6 result decrease of activity of kynureninaminotransferase that accompanied by decrease of its excretion with urine [18; 32]. Later Xanthurenic acid was found in urine of rabbits, dogs, guinea pigs and human [3, 11, 19–22].



5-OTDase — 5-tryptophanedehydrogenase; KATase — kynureninaminotransferase;
KATase-myt — kynureninaminotransferase mytochondrial; KYNase — kynureninase

Figure 1. Disturbances of Tryptophan Metabolism

Increasing of excretion of Xanthurenic acid with urine is revealed at elderly patients with diabetes mellitus. At elderly people [23] there is increase amount of Xanthurenic and of kynurenine acids in urine. In spite of the fact that administration of Pyridoxin result decreasing of concentration in urine, there is not a complete normalisation of their excretion [23]. Average concentration in daily urine at healthy persons fluctuates from 2.1 mg to 8.8 mg [12].

Deficiency of P-5-F in organism developed as result of deficiency of vit. B6 and as result of inhibition of synthesis of P-5-P from vit. B6. Synthesis of Xanthurenic acid is increased using of diet enriched by saturated fatty acids and of casein. Two enzyme systems are known which provide biosynthesis of P-5-F: pyridoxynphosphatoxydase (PPO) and pyridoxinkynase (PK). The diet enriched by fatty acids, stimulate decrease of activity of PPO in liver [24] which can be restored by administration of vit. B2, a co-enzyme of PPO. Studying of disturbamces of tryptophan metabolism depending on age of patients showed that in the first four days of life derivatives of kynurenine not found in the urine of newborns [25].

During the period from the 5th to the 20th day of life there are a minimal concentrations of Xanthurenic acid in urine. Administration of α-tryptophan does not increase excretion of Xanthurenic acid [26, 27], but in-

crease it at children at age of 4–6 years [28]. In patients age 70 years and over formation of kynurenine is increased. Administration of 100 mg/kg of α-tryptophan is accompanied by marked excretion of Xanthurenic acid. Administration of pyridoxine result normalization of excretion at elderly people [29]. There are a changes of tryptophan metabolism at pregnant women [30–32]. Administration of α-tryptophan accompanied by active excretion Xanthurenic acid with urine [33–35]. Administration of α-tryptophan, 100 mg/kg at pregnant women followed by increasing of excretion not only of Xanthurenic acid but also of kynurenine acid [36].

At the same time, the increase of excretion of Xanthurenic acid was found within all period of pregnancy and increase excretion of kynurenic acid was observed in the first 3 months [36; 82]. A high excretion of Xanthurenic acid at pregnant women was decreased after administration of Pyridoxine [33, 34; 83, 84]. The increased excretion of Xanthurenic acid — is a symptom of deficiency of vit. B6 in patients with diabetes [37, 38].

Very often disturbances of Tryptophan metabolism are shown as dissociation of Tryptophan accompanied by forming of a large amount of Xanthurenic acid. Deficiency of P-5-P result developing of disturbances of Tryptophan metabolism [14].

Y. Kotake in 1957 [4] investigated processes of formation and of excretion of Xanthurenic acid in organism. He used administration of various sodium salts of fatty acids and of Tryptophan. The most marked effect of endogene synthesis and excretion with urine of Xanthurenic acid — as 10.49 of mg daily — was showed using of complex as Tryptophan + oleic acid. The least effect — 1.6 mg — past using of Tryptophan only. Excretion of Xanthurenic acid after administration of Tryptophan in combination with fatty acid: Tryptophan + acetic acid — 5.37 mg; Tryptophan + propionic acid — 8.79 mg; Tryptophan + oil acid — 9.87 mg; Tryptophan + valerianic acid — 9.64 mg; Tryptophan + palmitinic acid — 9.61mg; Tryptophan + stearinic acid of — 8.57 mg.

The specific diet stimulate endogene synthesis of Xanthurenic acid was recommended by Y. Kotake [4]. Percentage of components of diet: casein — 22, salt mixture McCollumn — 6, agar-agar — 3, yeast — 2, oil — 10, sugar — 5, amylum — 52. This diet include the majority of above-named fatty acids in the structure and each diet caused increasing of excretion of Xanthurenic acid with urine by 3,5–6,5 times in compared with diet contain only Tryptophan. It was showed that biosynthesis of P-5-P depends of content of fat or fatty acids in diet. And as conclusion: diet enriched by fats result decreasing of activity of pyridoxalaminotransferase in liver [24]. Due to acceleration of kynurenine way of Tryptophan metabolism its diabetogenic metabolites can collect at a stress [39, 40].

Meanwhile injection of vit. B6 10.0 mg in experimental conditions result decreasing of excretion of Xanthurenic acid till 2.03 mg [42] per 24 h in compared with 8.42 mg without vit. B6. Y. Kotake in 1968 established that fatty acids suppress synthesis of P-5-P that result more active endogene synthesis of Xanthurenic acid. Intraperitoneal administration to mice of 200 mg/kg of endogene formed Xanthurenic acid followed by developing of diabetes [43]. It was showed a temporary hyperglycemia at rabbits after administration of Xanthurenic acid [44]. However, synthetic Xanthurenic acid, a dose of 200 mg/kg did not caused developing of diabetes in dogs and rabbits [45].

At the same time, a large amount of fat in diet in combination with Xanthurenic acid or kynurenic acid followed hyperglycemia and developing of histological changes typical for the experimental diabetes [10, 46–48]. Meanwhile disturbances of carbohydrate metabolism not developed in rats and rabbits after administration of Xanthurenic acid or containing of animals on free of vit. B6 diet [49].

Using of diet contains Tryptophan, 10 mg/kg in combination with hypovitaminosis of B2 [4] was followed by developing of hyperglycemia and xanturenuria.

At the rats contained on diet by Y. Kotake hyperglycemia is increased for long period that accompanied by glucosuria and and of polyuria. Animals had a tendency to increase of body weight on average from 140 g to 220 g and until 260 g (obesity) as of xanturenyria for 2–3 mg/24 h [50, 51].

It was established that increase of blood glucose level besides Xanthurenic acid is caused by kynurenine acid [52] which final products is quinaldine acid [53]. In our experiences with use within 3 months of a diet of Y. Kotake also permanent increase in level of a glycemia was revealed which was, however, less expressed in comparison with observed after single-pass administration of diabetogenic doses of other derivatives 8-oxyquinolines. Its influence by the end of experience was followed also marked — at 7–10 times — increasing of xanthurenuria and decreasing of insulin content in B-cells. Xanthurenic acid is transformed in 8-oxyquinaldinic acid [17] which possess diabetogenic properties. Other metabolites of Tryptophan as kynaldine and kynurenic acids possess insulin releasing activity [17, 50]. It is shown a large release of insulin from the isolated islets at the first 30 min. after the beginning of incubation.

Results of investigation of state of histostructure of pancreas of experimental animals: vacuolization and destruction of cytoplasm, hydropic distrophya, destruction of nuclei [4, 5, 54, 55–57].

It was established that increase of blood glucose level besides Xanthurenic acid is caused by kynurenie acid [58] which final products of metabolism is quinaldine acid [53].

Presence of quinaldine acid almost completely suppresses the second phase of release of insulin [59]. Incubation of insulin and of Xanthurenic acid result forming of stable complex [51, 60]. By using of fluorimetric methods it was showed that two moles of Xanthurenic acid connected with one insulin dimer. Hormonal activity of this complex decrease until 49 % of activity of native insulin [51, 61] and is increased past administration in media of Zinc [60, 62].

E.Murakami [63–65] showed that incubation of Xanthurenic acid with insulin result formation of two complexes. In one of them insulin is bound to 1 mole of Xanthurenic acid and in the second — with 1.5 mole. Xanthurenic acid easily formed complex with insulin in blood serum, without breaking structure of insulin. This complex is stable [51]. It was supposed that chemical connection is carried out between atom of Zinc and imidazole radical in a molecule of insulin [51, 43]. Xanthurenic acid shows a high affinity for ions of Zinc [66]. Activity of insulin is restored after addition of ions of Zinc to blood serum contains of complex XA-insulin [67].

Presented data about diabetogenic properties of Xanthurenic acid are interesting first of all that contrary for other diabetogenic chemicals, Xanthurenic acid is synthesised in human and animals at disturbances of diet in combination with deficiency of Pyridoxin.

On the mechanisms of diabetogenic activity of Xanthurenic acid

More than 60 years ago Y. Kotake noted a strong likeness of chemical structure of molecule and of properties of Xanthurenic acid with other diabetogenic derivatives of 8-oxyquinoline (Fig. 2). He supposed that diabetogenic properties of Xanthurenic acid determined by the –OH radical located in position «8» of the molecule of Xanthurenic acid [68, 69]. Xanthurenic acid possess a high affinity for ions of Zinc [66]. In 1957 Y. Kotake and M. Kato confirmed that Xanthurenic acid possess diabetogenic properties only in case if –OH radical is fixed in the position «8» of a quinoline ring similar as other diabetogenic derivatives of 8-oxyquinoline (Fig. 2). Extraction or replacement of it followed by complete disappearing of diabetogenic properties of Xanthurenic acid [54, 69].

G. Weitzel and coll. confirmed [45] that Xanthurenic acid form with Zinc a chelate complex 1:1 and atom of Zinc is fixed between hydroxyl and carboxylic groups of a quinoline ring (Fig. 2). It is known that such type of complex of metal with derivatives 8-oxyquinolines is the most toxic for cells. E. Murakami and Y. Kotake investigated interaction between insulin and Xanthurenic acid. For the first time the evidence of ability of Xanthurenic acid to connect insulin in experiences of in vitro were presented by E. Murakami [65].

On the base of obtained results, Y. Kotake, T. Ueda and coll. (1975) proposed a follow mechanisms of diabetogenic properties of Xanthurenic acid (Fig. 3, left part).

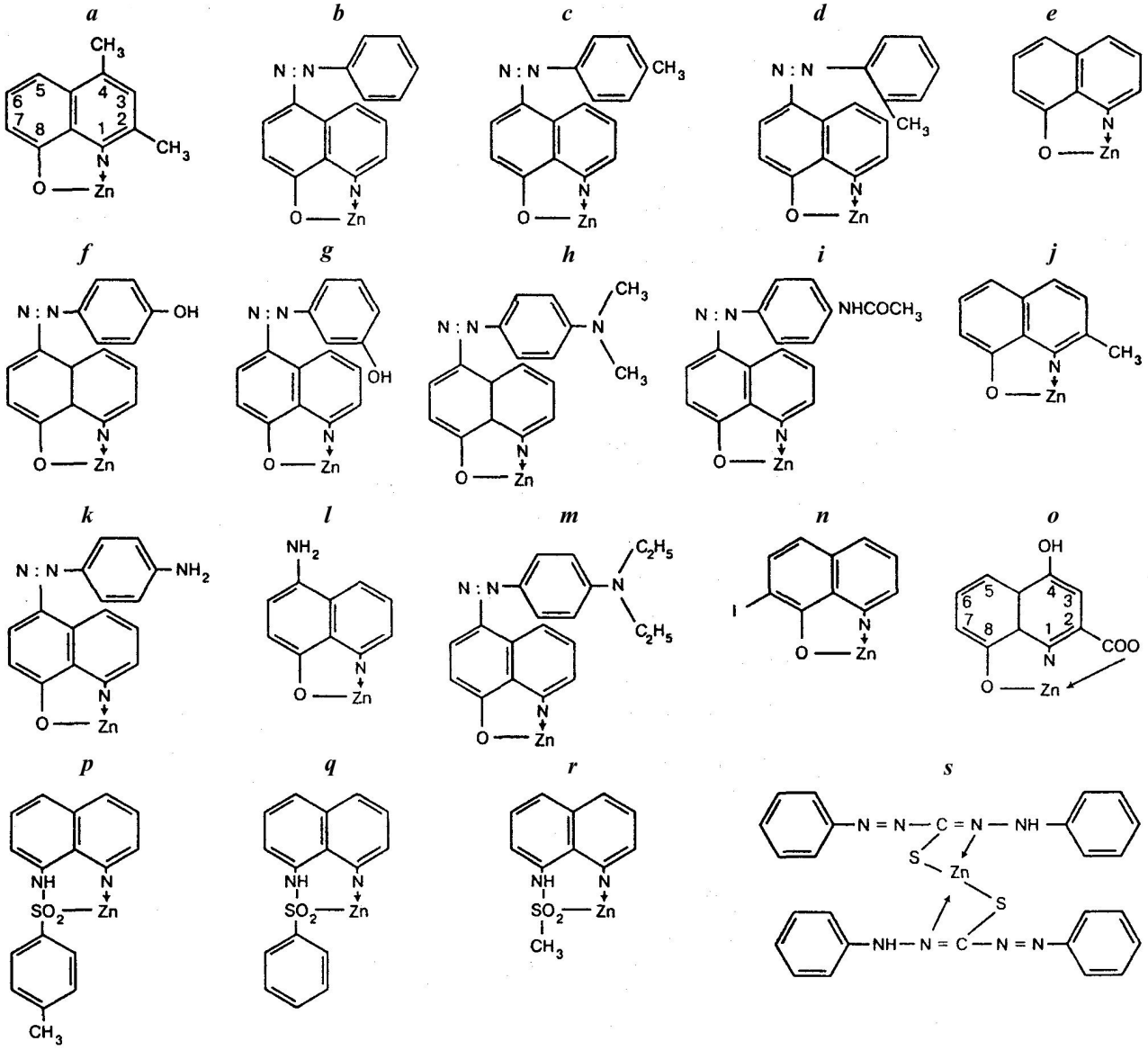
Meanwhile, T. Ueda and coll. [70] found that after dissociation of complex XA-insulin a new complex as XA-Zinc is formed. However attention to this fact was not given and this ability was not investigated. In experiences of in vitro it was shown that Xanthurenic acid interact with Zinc in B-cells that accompanied by damage of cells [57, 71, 72].

Deficiency vit. B6 stimulate metabolisation of Xanturenic acid for final product as 8-oxyquinaldinic acid whereas kynurenic acid metabolised into quinaldine acid. Both of these acids possess insulin releasing properties on model of isolated islets [50]. On the other hand, these metabolits slow down formation of B-granules as result of blocking of ions of Zinc in B-cells. 8-oxyquinaldine acid suppress proinsulin synthesis whereas kynurenic acid is in this regard less effective [69]. Besides, Xanthurenic acid slows down synthesis of insulin as a result of inhibition of binding of insulin with Zinc [28].

Disturbances of Tryptophan metabolism: as final product of metabolisation of Xanthurenic acid can be collected 8-oxyquinaldine which possess diabetogenic properties and caused hyperglycemia and developing of degenerative changes in islets [70]. Meanwhile, still nobody found this substance in blood, urine or in other biological liquids of animals. Nevertheless, it is impossible to exclude a possibility of its accumulation in an organism at disturbances of Tryptophan metabolism.

Diabetes caused by derivatives 8-oxyquinoline can be prevented by preliminary binding of Zinc by not diabetogenic chelat active chemicals or by elimination of Zinc from B-cells before action of diabetogenic ligands that protect B-cells in 90–95 % of animals of destruction for 12–24h. Meanwhile such method have not perspectives for practical application as well as method based on elimination of Zinc from B-cells: it is

almost impossible to keep Zinc ions in B-cells permanently in complex with not dia- betogenic ligands as well as to eliminate Zinc from B-cells for immeasurable period. Meanwhile, it is known that endogene synthesis of Xanthurenic acid principally may be supressed by compensation of deficiency of Pyridoxine in organism which is one of main causes of endogene synthesis of Xanthurenic acid.



a) 2,4-dimethyl-8-oxyquinoline, 35 mg/kg; *b*) 5-phenylazo-8-oxyquinoline, 20 mg/kg; *c*) 5-para (toluene)-8-oxyquinoline, 20 mg/kg; *d*) 5-orto(toluene)-8-oxyquinoline, 40 mg/kg; *e*) 8-oxyquinoline, 50–60 mg/kg; *f*) 5-para(diethylaminophenylazo)-8-oxyquinoline, 20 mg/kg; *g*) 5-meta(hydroxyphenylazo)-8-oxyquinoline, 30 mg/kg; *h*) 5-para(dimethylaminophenylazo)-8-oxyquinoline, 45 mg/kg; *i*) 5-para-(acetylaminophenylazo)-8-oxyquinoline, 50 mg/kg; *j*) 8-oxyquinaldin, 10 mg/kg; *k*) 5-para(aminophenylazo)-8-oxyquinoline, 10 mg/kg; *l*) 5-amino-8-oxyquinoline, 30 mg/kg; *m*) 5-para(diethylaminophenylazo)-8-oxyquinoline, 40 mg/kg; *n*) 9-oxy-7-iodoquinoline, 50–60 mg/kg; *o*) 4,8-dihydroxyquinolin-2 carboxylic acid (Xanturenic acid); *p*) 8-para(toluenesulphonylamino)quinoline, 30–50 mg/kg; *q*) 8-para(benzolsulphonylamino)quinoline, 30–100 mg/kg; *r*) 8-para(metansulphonylamino)quinoline, 40–81 mg/kg; *s*) diphenylthiocarbazone (dithizon), 45–50 mg/kg

Figure 2. Complex salts of Diabetogenic zincbinding chelat active chemicals with Zn-ions and its diabetogenic doses

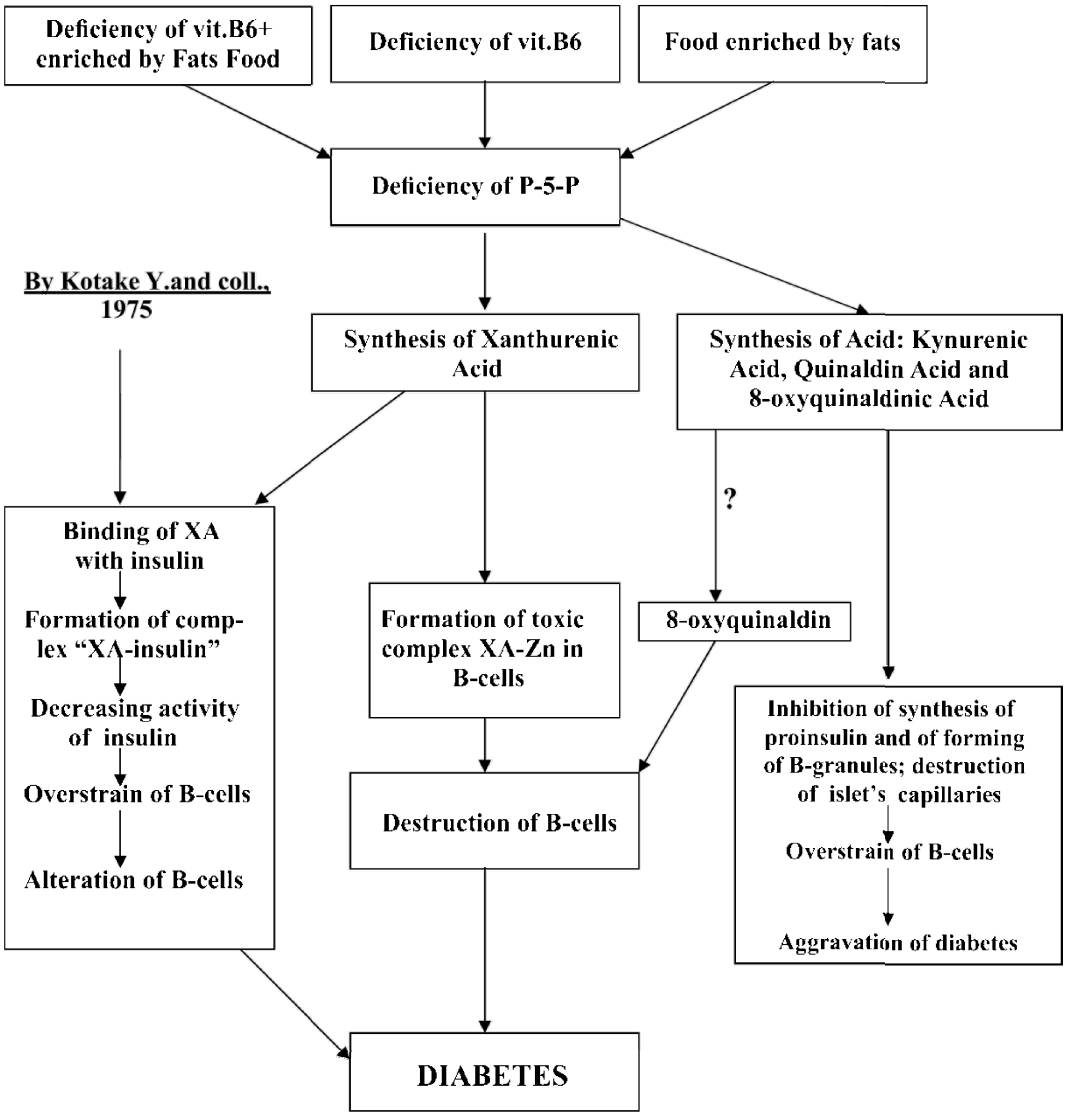


Figure 3. Mechanisms of Diabetogenic Activity of Xanthurenic Acid

As result of disturbances of Tryptophan metabolism the 8-oxyquinaldine may be accumulated in organism. Meanwhile 8-oxyquinaldine, a derivative of 8-oxyquinoline, is diabetogenic chemical which are able to induce hyperglycemia and degenerative changes in B-cells. However XA is eliminated from the organism with urine and now there are not reported facts that XA is transformed in 8-oxyquinaldine in organism. Nevertheless, we cannot to exclude this possibility.

These methods protection of B-cells which we have used in our investigations of mechanisms of developing of diabetes induced by chelat active chemicals, not have perspective for practical using because it is not possible and not expediently to keep Zn-ions in B-cells permanently connected with not diabetogenic substances or to eliminate permanently Zn-ions from the cytoplasm of B-cells or to keep cells free of Zn-ions permanently.

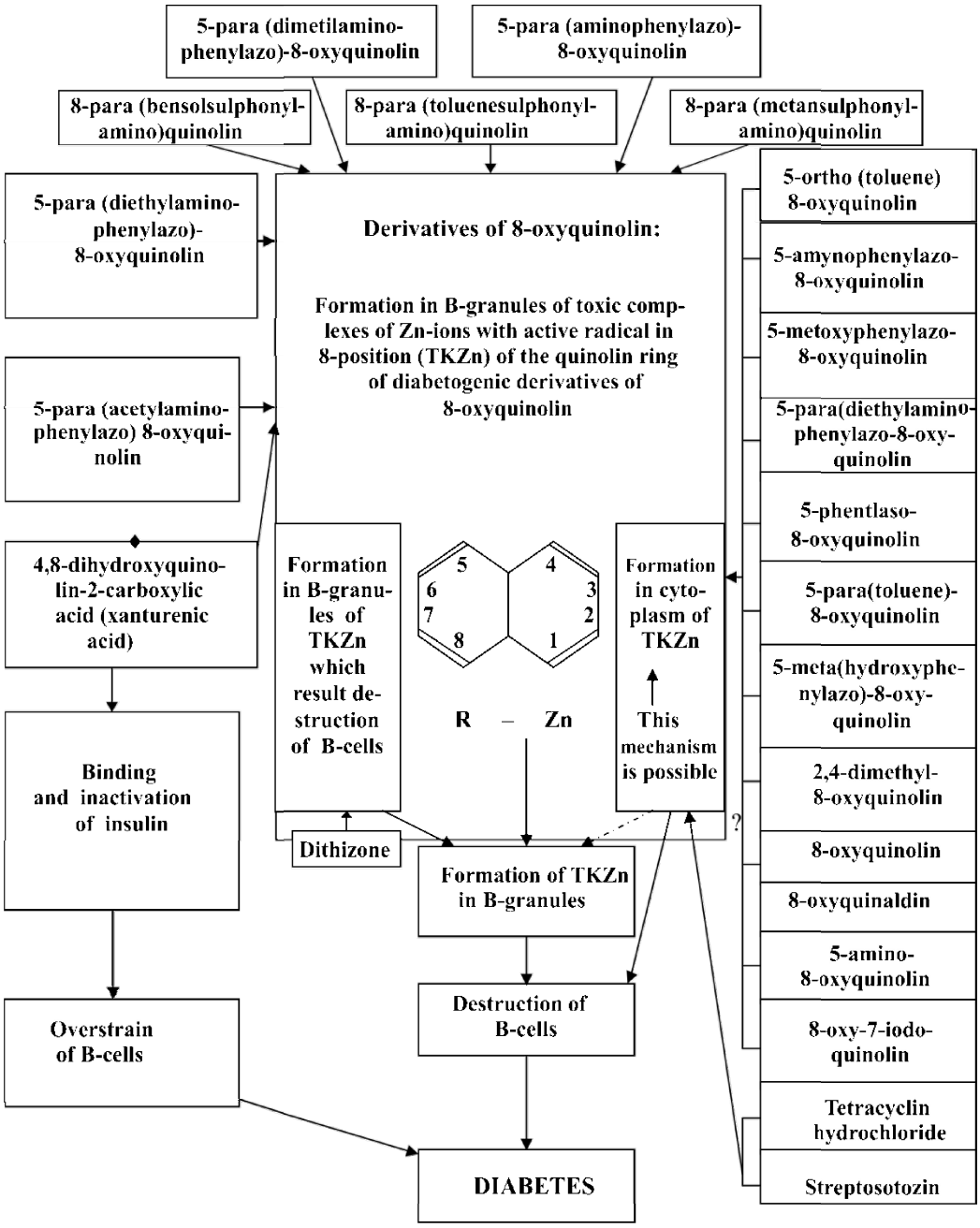
Thus, despite of fact that by aid of both methods is possible to prevent developing of experimental diabetes in 95–100 %, these methods are not suitable for protect of B-cells of XA-diabetes in human.

Now it is possible to suppose that among all metabolits of abnormal Tryptophan metabolism the main role is belong to XA. Other metabolits of tryptophan are able to aggravate diabetes induced by XA.

However it is known that synthesis of XA in organism may be prevented by administration of vitamin B6. This way for prevention developing of XA induced diabetes is, as we think, more perspective. Besides this method not need additional researches regarding practical using of vitamin B6.

Injection of other diabetogenic derivatives of 8-oxyquinolin (Fig. 2) result a few days later developing of heavy 1 type diabetes due to ability to form into cytoplasm of B-cells of toxic chelat complexes that result destruction of cells within 15–30 min. and developing of diabetes (Fig. 4, 5). Diabetes induced by XA in the

contrary developed like diabetes of 2 type. It is explained by a followed circumstances. Other diabetogenic derivatives of 8-oxyquinolin were used as one injection of diabetogenic doses of substance. In the contrary, more less amount of XA is formed in human more slowly, day by day permanently as changes of Tryptophan metabolism especially in old organism.



♦ — synthesized in human

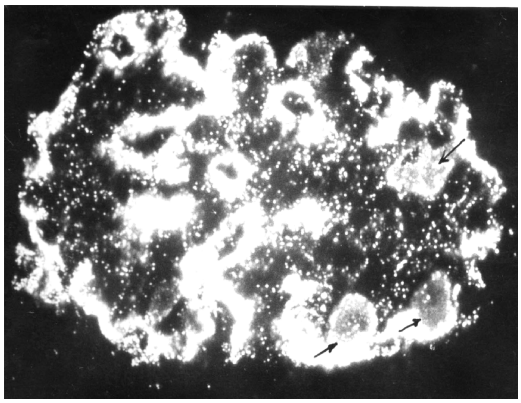
Figure 4. Mechanisms of damage of B-cells caused by diabetogenic chelat active chemicals

Interest to diabetes induced by XA is increased due to followed factors:

1) XA in the contrary to other diabetogenic derivatives of 8-oxyquinolin is formed in human organism as result of disturbances of diet in deficiency of vit. B6;

2) a large amount of XA is discovered in the urine not only of diabetic patients in middle or old age, but in the urine of persons in same age without diagnosis of diabetes;

3) deficiency of vitamin B6 is discovered in organism of old persons with registrated diagnosis of diabetes or without it.



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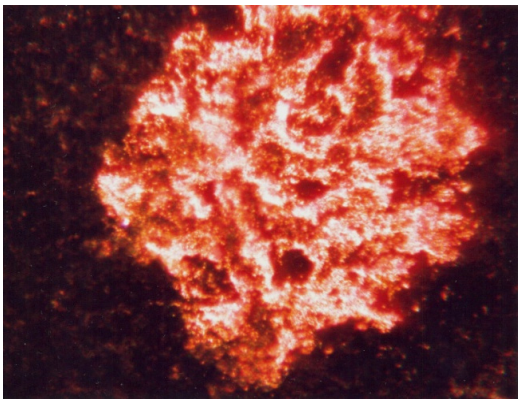

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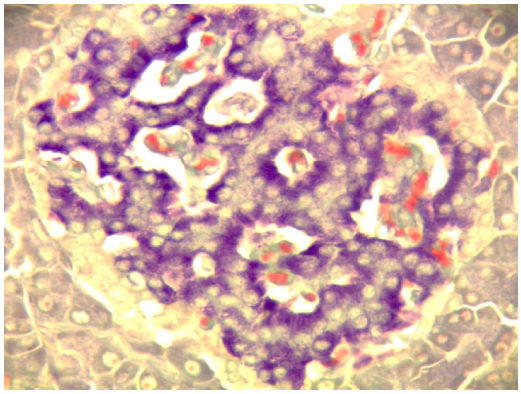

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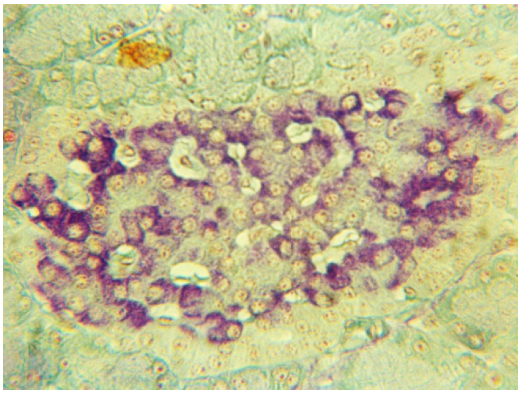

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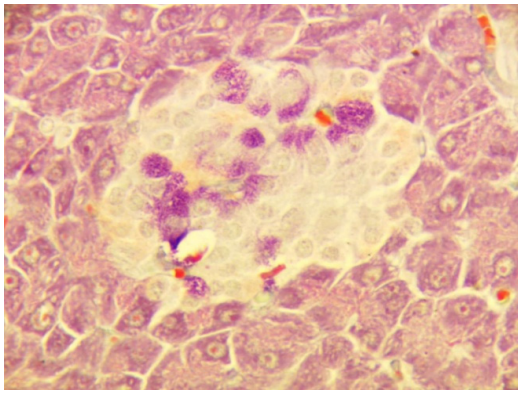

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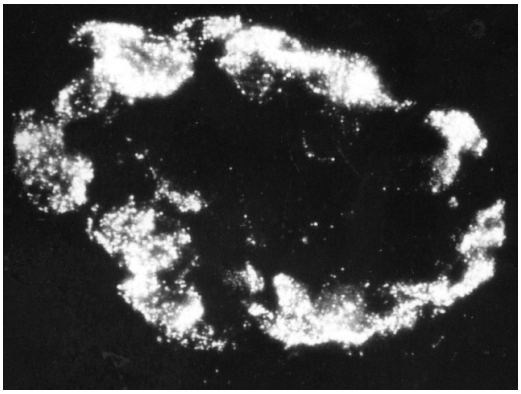

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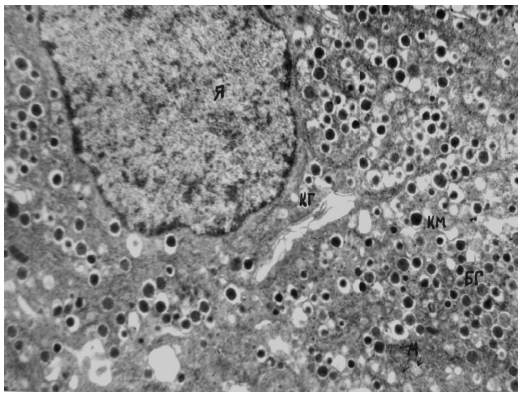

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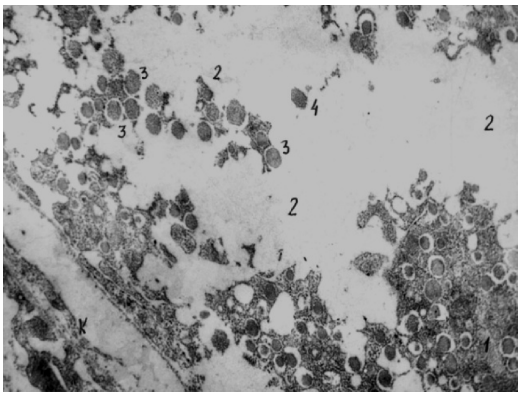

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1 — Intact Rabbit. Injection of Ditizon (DZ), 31 mg/kg. Granules of complex Zn-DZ concentrated around capillaries; frozen section, 4 mcm; darc condensor; ×280; preparat and photo — by Meyramov G.G., 1964;

2 — Intact Rabbit. Injection of Ditizon (DZ), 50.6 mg/kg. Large amount of granules of complex Zn-DZ in cytoplasm of B-cells; frozen section, 5 mcm; darc condensor; ×280; preparat and photo — by Meyramov G.G., 2012;

3 — Intact Rat. Aldehydefucshin. Maximal concentration of violet granules of zinc-insulin depot form of insulin in B-cells around capillaries; ×280; preparat and photo — by Meyramov G.G., 2008;

4 — Rat with diabetes induced by endogen synthesized of XA. Aldehydefucshin. Destruction and degranulation of B-cells in central part of islet; ×280; preparat and photo — by Meyramov G.G., 2001;

5 — Rat with diabetes induced by streptosotozin, 34 mg/kg. Aldehydefucshin. Destruction and degranulation of B-cells; ×280; preparat and photo — by Meyramov G.G., 1998;

6 — Rabbit. Diabetes induced by Dithizon, 50.2 mg/kg; frozen section; darc condensor; ×280; complete destruction of B-cells in islet 30h past injection of DZ; preparat and photo — by Meyramov G.G., 1972;

7 — Intact B-cell of Rabbit. Transmission electron microscopy. Cell matrix without changes; a large amount of B-granules in cytoplasm; ×4450; preparat and photo — by Meyramov G.G., 1973;

8 — B-cells of Rabbit 2h past injection of Dithizon, 49.6 mg/kg. Transmission electron microscopy; 1 — destruction of cell matrix on 85–90 % of cell's surface; 2 — zones of cytoplasm free of matrix; 3, 4 — destroyed B-granules in zones free of matrix; ×5650; preparat and photo — by Meyramov G.G., 1973

Figure 5. Histostructure and ultrastructure of pancreatic islets in animals with diabetes caused by zincbinding chemicals (ditizon and xanthurenic acid)

Previous our investigations of mechanismes of diabetogenic action of derivatives of 8-oxyquinolin, which cannot be synthezed in organism or to come into organism outside, have theoretical significance only. However data obtained during these experiences let us to understand more profoundly mechanisms of diabetogenic action of XA. XA due to noted above data make us to keep our attention on this substance which may to have significance in pathogenesis of human diabetes.

On the base of data obtained by other investigators and by us is proposed a followed point of view on the mechanisms of diabetes induced by XA **(**Fig. 3**)**.

Thus, noted above data show a potential role of diabetogenic metabolits of tryptophan in the pathogenesis of human diabetes. From presented data it is possible to conclude that main role among a few metabolits as XA, kynurenic acid, oxyquinaldic acid, 8-oxyquinaldinic acid and 8-oxyquinaldin — are belong to XA. Kynurenic acid and oxyquinaldic acid not contain, in the contrary to XA, in position 8 of quinoline ring of active chemical group and not induced diabetes. But both these chemicals activate releasing of insulin from B-cells.

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Триптофанның диабетогендік метаболиттері

Мақалада бүгінгі таңда 30-дан астам заттардың ішінде диабетогендік химиялық заттың бірі болып табылатын, басқалардан ерекшелігі — ересек жастағы ағзада ғана түзілуге қабілетті, триптофан аминқышқылдарының алмасу өнімдерінің диабетогендік әсер ету механизмі және зерттеу әсеріне қатысты әдеби деректерге сараптама, өзіндік зерттеулер нәтижесі келтірілген. Авторлар ксантурен қышқылының гистоқұрылым күйін және В-жасушалардағы инсулин құрамын бұзу механизмдерін жан-жақты зерттеген. Осы заттар арқылы туындайтын диабетті болдырмаудың мүмкін жолдары, сонымен қатар ағзада эндогенді синтезделуді неғұрлым нақтырақ бәсеңдету жолдары жан-жақты қарастырылған.

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Диабетогенные метаболиты триптофана

В статье даны обзор и анализ литературных данных, а также результаты собственных исследований, касающихся изучения характера и механизмов диабетогенного действия продуктов нарушенного обмена аминокислоты триптофана. Она является единственным диабетогенным химическим веществом из более чем 30 известных на сегодня, которое способно, в отличие от всех других, синтезироваться в организме, особенно лиц старшего возраста. Авторами исследованы механизмы повреждающего действия основного из них — ксантуреновой кислоты, характер ее действия на состояние гистоструктуры и содержание инсулина в В-клетках. Исследованы возможные пути предотвращения развития диабета, вызываемого этим веществом, на основе чего обоснован наиболее реальный способ подавления эндогенного синтеза в организме данного вещества.

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