Vascular changes in pancreas in diabetes caused by abnormal metabolits of tryptophan aggravate developing of diabetes

Contrary to many models of experimental diabetes caused by chemicals, diabetes induced by endogene synthesis of xanturenic acid (XA), a metabolit of abnormal Tryptophan metabolism, approached to human diabetes. Meanwhile in these conditions of natural developing of diabetes not in result of artificial injection of diabetogenic substances, are not investigated yet state of blood vessels and blood circulation as in exocrine pancreas tissue as in pancreatic islets. Authors showed developing in experimental XA-diabetes of numerous destructive changes of blood vessels of a pancreas, fibrinoid changes of parenchyma of pancreas tissue, dystrophy and necrosis of exocrine and endocrine pancreas tissue; necrotic changes of endothelium of arteries. In pancreatic islets: necrosis of endothelium and cells in peri capillar. Authors conclude that described changes can result aggravation of developing of diabetes.

Key words: diabetes, pancreas, exocrine tissue, B-cells, vascular changes.

The main cause for mortality of patients with type 2 diabetes are cardiovascular complications [1, 2]. The leading role in development of these complications belongs to a hyperglycemia which is a cause of a number of pathological processes such as endothelial dysfunction, oxydative stress, changes of rheological properties of blood in macro- and microvessels [3]. It was reported that thickening of basal membranes is developed in capillaries as result of fixation on the endothelium of vessels of amorphous material consisting mainly of mucopolysaccharides [4]. It is known that microcirculation in diabetes accompanied by aggregation of blood cells and damage an endothelium. Sclerosis, inflammation and destruction of vessels result developing of heavy blood circulation [5].

Research objective: to study state of histostructure of blood and of stroma of tissue of pancreas in experimental Xanthurenic acid induced experimental diabetes.

Materials and methods

Diabetes in animals caused by containing of animals on diet by Y.Kotake [6] stimulated endogene synthesis of 4,8-dihydroxyquinolin-2-carboxylic acid (Xanthurenic acid, XA) which possess diabetogenic properties due to direct selective destruction of B-cells as to binding and inactivation of insulin [6]. 72 white rats Vistar 160–240 g. body weight were used. Animals were distributed for 5 groups. Rats of Groups 1, 2 and 3 were contained 60, 90 and 120 days respectively on a diet stimulated endogene synthesis of XA. The diet components included starch, butter, sugar, casein, yeast and salt additives. Group 4 (diet+vit. B6), investigation of blood Glucose concentration and of Xanturenyria excluding histological and histochemical analysis of pancreas tissue: animals were treated within period of containing on diet by injections of water solution of vit. B6 8,7 mg/kg per day. Group 5 (control 2) — intact animals. Blood Glucose control-weekly by Glucose oxydase method. Concentration of Xanturenic acid in urine [7] was measured monthly and body weigh in the beginning and at the end of experience.

Histology. Samples of pancreas tissue fixed in Bouin liquid, carried out in alcohols 70º, 80º, 90º and 100º, filled in paraffin. Leica 2125 rotation microtome used for preparing sections 4–5 mcm. For survey microscopy of tissue of a pancreas staining technology was applied using hemalaoun of Mayer and eosin [8] as hemathein of Mayer [9].

Results

Blood Glucose level. 60 days containing of rats on diet: increasing of blood Glucose level for 1,5–1,8 times in majority of number of animals excluding 6 rats have kept normal value. On average level of a glycemia is 6,91 ± 0,36 mmol/l (p ≤ 0,05) in compared with initial 4,20 ± 0,11 mmol/l (Fig. 1). On 90th day containing on diet blood Glucose level is increased for 1,9 times comparatively with initial (p ≤ 0,001). In some animals increasing for 2,5–3 times was observed. 4 rats have not changes of blood Glucose level. We observed till 90th day decreasing of body weight of experimental animals on the average from 216,84 ± 4,07 g to 183,20 ± 4,06 g (p ≤ 0,001).

At 120th day of experience concentration of blood Glucose level was increased for 2,8–3 times on average, until 11,81 ± 0,56 mmol/l (p ≤ 0,001) comparatively with initial 4,11 ± 0,19 mmol/l by 2,8–3 times; p ≤ 0,001. The body weight was decreased for 23–25 %; (p ≤ 0,001) comparatively with initial.

The analysis of level of xanturenia of rats contained on a diet for 120 days showed reliable increase in compared with control for 9–10 time (p < 0,001) (Fig. 2). Thus, the maintenance of animals on diet accompanied by development of marked hyperglycemia reaching the maximum till 120 day.
Morphological researches

30th days containing on diet result developing of: disturbances of blood circulation; fibrinoid changes of intraglobular arteries of exocrine tissue; necrosis of veins, destroying of vessel’s wall, hemostasis, lysis and infiltration of eritrocytes in tissue (Fig. 3.1); distribution of fibrinoid processes to parenchyma.

3.1 — Pancreas tissue. Stasis and hemolysis in interglobular arteries (→). Destruction and necrosis of connecting tissue of blood vessels (→→→). 30 days on diet. Staining by Victoria 4R; ×280;

3.2 — Pancreas tissue. Fibrinoid changes of arteries (→). Necrosis of veins (→→→) and distrophia of ductus (→→→→). 60 days on diet. Staining by Hemalaoune and eosin; ×280;

3.3 — Pancreas tissue. Stasis and hemolysis in interglobular vein (→). Fibrinoid changes, destruction of acinuses and atrophy of exocrine parenchyma (→→→→). 60 days on diet. Staining by Hemalaoune and eosin; ×280;

3.4 — Exocrine tissue of pancreas. Growing of collagen fibers in globules (→). Hyposis in inter acinuses spaces and collagen fibers around acinuses (→→→). 60 on diet. Staining by Victoria 4R; ×700;

3.5 — Pancreatic islet. Marked hyperemia and lysis of eritrocytes in capillaries (→→→). Degranulation and destruction of B-cells (→→→). 60 days on diet. Staining by Aldenye Fushine and Helmi; ×700;

3.6 — Pancreatic islet. Degranulation of B-cells (→). Distrophia and necrosis of B-cells (→→→). Thrombosis of veins (→→→→). 100days on diet. Staining by Aldenye Fushine and Helmi; ×280;

3.7 — Pancreatic islet. Destruction of internal capsule (→) and hyalinosis on middle and external capsules of arteries (→→→). 120 days on diet. Staining by Victoria 4R; ×280;

3.8 — Pancreas tissue. Dissociation of acinuses (→). Destruction of islets, necrosis of B-cells (→→→). 120 days on diet. Staining by Hemalaoune and eosin; ×280

Figure 3. State of pancreas tissue and vascular changes in exocrine and endocrine tissues

60th days containing on diet accompanied by: developing of destructive changes in parenchyma (Fig. 3.2); hyperemia and destruction of capillaries; growing of collagen fibers accompanied by necrosis of adventicium of vessels; necrosis of veins with infiltration of eritrocytes in tissue; fibrinoid changes in parenchyma of tissue, fat infiltration and fat necrosis of the gland’s cells; intraglobular fibrillogenesis; infiltration of parenchyma by collagen fibers (Fig. 3.4); hemostasis and lysis of eritrocytes in capillaries of islets (Fig. 3.5). Arterioles: fibrinoid changes, thickening of walls. Venules: necrosis, destruction, infiltration of eritrocytes in tissue. Fibrinoid changes of stroma of pancreas, growing of fat tissue in interseptal spaces;
pressing of acinues by fat tissue and forming of necrosis centers in gland’s tissue; developing of intraglobular 
fibrillogenesis that accompanied by thickening of interstitium of pancreas tissue. Infiltration of paren-
chyma by collagen fibers, dissociation of parenchyma for little gland segments consisting of a few acinuses 
(Fig. 3.4).

90 days containing on diet result: hemorrhagic necrosis of exocrine tissue, sclerosis of wall of arteries; 
growth of fibrous structures; sclerosis of capillaries. Hyperemia in veins and in capillaries; fibrinoid changes 
of arterioles; thickening of basal membrane of endothelium; stagnant hyperemia in vessels of venous collect-
or; alteration of arterial endothelium, destruction of endothelial layer in arteries and in interglobular veins, 
proliferation of facile muscle cells; destruction and distrophy of walls of vessels, infiltration in tissue of 
components of blood; sclerosis and inflammation, concentration of leucocytes in the gleam of vessels and 
imfiltration of parenchyma of tissue- 
sue; growing of fat tissue in islets with degranulation, distrophy and necrosis of B-cells, stasis and hemolysis in capillaries of islets (Fig. 3.6); infiltration of lymphocytes and leuco-
cytes outside of vessels, homogenization of blood cells in vessels; thrombosis of veins and capillaries; de-
veloping of hyalinosis in arteries (Fig. 3.7); destruct- tion, distrophy and incapsulation of acinuses; agglomera-
tion of fibroblasts, lymphocytes and collagen fibers nearest destroyed acinuses. Near vascular bunches, is-
lands and of acinuses; the wide cavities, filled by homogeneous consistence liquid near vascular bunches as 

near island (Fig. 3.8).

100–120 days containing on diet. Inflammation of arteries and veins, infiltration of leucocytes outside 
of arteries and veins parenchyma; necrosis of parenchyma, growing of fat tissue accompanied by 
intraglobular lipomathosis; islets: marked hyperemia, stasis in capillaries, degranulation and necrosis of 
B-cells (Fig. 3.6); marked hyperemia in veins in combination with infiltration of lymphocytes into the wall 
of vessels; gomogenisation of collagen fibers in adventicium of arteries, concentration of fibroblasts between 
collagen fibers.

Thus, disturbances of metabolism in animals contained on diabetogenic diet result marked destructive 
changes in arteries, veins and capillaries as in islets as in exocrine tissue of pancreas that accompanied by 
destruction of walls of vessels and fibrinoid changes of stroma. Noted above changes accompanied by dis-
turbances of circulation of blood in vessels and by hemostasis which is estimated as sign of acute pathologi-
ical process [3.3].

Stasis is a frequent effect in disturbances of cardiovascular system and of blood circulation caused by 
external causes [16]. J.Andersen and coll. [17] supposed that accumulation in their wall of fibronectin, of 
type 4 collagen, hyaluronic acid and calcium result damage of blood vessels. Dysfunction an endotelium ac-
companied by angiospasm, thrombosis and tendency for developing of atherosclerosis [18, 19]. Insulin re-
sistance is estimated as one of cause of destruction of blood vessels [20]. On 30th day containing on diet we 
observed accumulation of fats in wall of interglobular arteries and developing of lipomathosis in globules. 
Diabetes accompanied by marked forms of this processes as by fibrosis and lipomathosis of intraglobular 
spaces [21].

Dysfuction of endothelium is shown by angiospasm, tendencies for formation of thrombs and develop-
ing of atherosclerosis [19].

Thus, at first week of experience disorders of blood circulation and destructive changes of vessels were 
developed and accompanied by fibrinoid changes, fibrosis and lipomathosis in intraglobular spaces. Stagnation 
and long time prolonged hemostasis result destruction of vessel’s wall and exit of eritrocytes in exocrine 
tissue. Formation of blood clots is a symptom of chronic process. Vascular changes, result developing of nec-
rosis in acinuses and of atrophya of exocrine tissue of pancreatic islets. Proliferation of epithelial tissue and 
periuctal sclerosis of gland’s ductus as hemorrhagic sclerosis of exocrine tissue cells with sclerosis of capil-
laries walls are estimated as structure symptoms diabetes mellitus [16, 21].

As it was observed in pancreas sections of rats contained on a diet from the 30th till 120th days, sclero-
tic changes underwent some stages of development: from plasmatic infiltration and fibrinoid changes of a 
wall of vessels to hyalinosis. Hyalinosis of small arteries and the capillaries, developing as result of plasmat-
ic infiltration is widespread at diabetes and most expressed in a brain, a kidney, in retina and islets.

Thus, analysis of results of research of series of experience showed accruing suppression of function of the 
B-cells, accompanied by degenerative changes and decreasing of insulin content in cytoplasm of B-cells 
for 76 % caused by XA.

Developed multiple wascular changes in blood vessels as in pancreatic islets as in exocrine tissue result 
developing of fibrinoid changes, of sclerosis of stroma including hyalinosis of arteries and sclerosis of capil-
laries and veins. These changes aggravate developed diabetes in spite of the fact that are not its direct cause.
Acknowledgement

Authors are thankful to Prof. G.G. Meyramov, head of Diabetes Research Centre, Karaganda, for supporting this investigation.

References

А.А.Кикимбаева, А.М.Тулиева, А.А.Жуужасарова, А.Е.Моращ, Р.С.Мамитхан, Г.Д.Дилдабекова

Нарушения кровообращения при воздействии на организм диабетогенных метаболитов триптофана, усугубляющее течение экспериментального сахарного диабета

При экспериментальном ксантуреновом диабете, который по характеру развития и течения приближается к диабету у человека, авторы исследовали развивающиеся деструктивные изменения кровеносных сосудов поджелудочной железы. Они сопровождаются фибриноидными изменениями паренхимозной ткани, т.e., в свою очередь, дистрофией и некрозом эндо- и эндокраниной ткани. В инкретных островках выявлены деструкция эндотелия капилляров и некротические изменения перикапиллярных B-клеток. Авторы полагают, что сосудистые изменения, не являясь прямой причиной диабета, могут значительно утяжелять его течение.

References