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PROTEOLYTIC PLASMA ACTIVITY IN DIABETIC PATIENTS WITH CHRONIC IMPAIRMENT OF CEREBRAL CIRCULATION

Summary. Diabetic patients with chronic impairment of cerebral circulation underwent measurement of the indices of plasma proteolytic activity. The inhibition of proteolytic destruction of low- and high-molecular proteins, accompanied by intensification of collagenolysis, was established, indicating the intensity of destabilization of cerebral atherosclerotic plaque. The obtained changes progressed with the stage of encephalopathy.

I. Introduction.

Diabetic encephalopathy (DE) is thought to be one of the most frequent and certainly most troubling and life-threatening chronic complications of diabetes mellitus (DM), which affects the quality of patients' life, leads to the earlier invalidity, stipulates the development of mental disturbances, etc. Thus, individuals with type 2 DM have 2-6 times higher incidence rate of cerebral strokes and 2-4 times greater mortality rate from cardio-vascular events [3].

Such abnormalities, as hyperglycemia, hyperinsulinemia (endo- and exogenous), insulin resistance, altering myoinositol mechanism, activating sorbitol (polyol) pathway, accelerating nonenzymatic glycosylation of proteins, leading to tissue hypoxia and overproduction of insulin-like and other growth factors, accompanied with hemodynamic disturbances and carbohydrate, lipid, protein metabolic disorders, etc., have been postulated to be principal pathogenic factors in the development of DE [4]. Nevertheless, the processes of plasma fibrinolysis and proteolysis in patients with DE, depending on its stage, haven't been displayed by other investigators.

II. Aim.

The objectives of our study were to reveal the peculiarities of plasma proteolytic activity in diabetic patients with chronic impairment of cerebral circulation. To accomplish this, the study concerned a group of 65 patients with DE and 14 healthy nondiabetic individuals, who served as control group. Stage I DE was diagnosed in 23 patients of studied group, stage II and III – in 25 and 17 patients respectively. The diagnosis of DE was made on the basis of patients' complaints, anamnestic findings, results of endocrinological and neurological inspection, mental state examination, data, obtained by means of Doppler analysis of major cerebral arteries, computerized tomography and magnetic resonance scanning techniques, routine laboratory studies. Proteolytic plasma activity was determined with the use of azosubstrates, produced by "Simko" Ltd. (Ukraine): azoalbumin (lysis of low-molecular proteins), azocasein (lysis of high-molecular proteins) and azocol (collagenolysis) [2]. Statistical analysis of the results was performed by means of Biostat software, using Student's t-criterion.

III. Results.

The study of proteolytic plasma activity in case of DE demonstrated significantly decreased lysis of low-molecular proteins by 21,7%, accompanied by elevated collagenolysis by 16,9%.

Furthermore, the indices of proteolytic activity on I stage of the disease were also similar to those in the group of healthy participants. Lysis of low-molecular proteins was significantly reduced (20,4%) in patients with stage II DE.

The rate of proteolytic destruction of high-molecular proteins tended to that of the controls (no statistical significance was found) (Table).

Table Characteristics of plasma proteolytic activity indices in patients with diabetic encephalopathy in dependence on its stage (M±SE)

Indices	Group, number of examined patients				
	Control, n=25	DE, n=65	Stage I DE, n=23	Stage II DE, n=25	Stage III DE, n=17
Lysis of low-molecular proteins, mkg of azoalbumin/ml at 1 hour	2,40±0,09	1,88±0,08 $P_1<0,001$	2,14±0,13 $P_1>0,05$	1,91±0,12 $P_1<0,01$ $P_2>0,05$	1,47±0,10 $P_1<0,001$ $P_2<0,001$ $P_3<0,05$
Lysis of high-molecular proteins, mkg of azocasein/ml at 1 hour	1,70±0,06	1,52±0,06 $P_1>0,05$	1,63±0,09 $P_1>0,05$	1,49±0,11 $P_1>0,05$ $P_2>0,05$	1,41±0,09 $P_1<0,01$ $P_2>0,05$ $P_3>0,05$
Collagenolysis, mkg of azocol/ml at 1 hour	0,71±0,03	0,83±0,04 $P_1<0,05$	0,72±0,04 $P_1>0,05$	0,78±0,04 $P_1>0,05$ $P_2>0,05$	1,08±0,09 $P_1<0,001$ $P_2<0,001$ $P_3<0,01$

Note: values are expressed as mean with their standard errors;

P – coefficient of statistical significance;

P_1 – significant difference in comparison with control ($P\leq0,05$);

P_2 – significant difference in comparison with group of the patients with stage I DE ($P\leq0,05$);

P_3 – significant difference in comparison with group of the patients with stage II DE ($P\leq0,05$).

Stage III DE exhibited the most profound changes of plasma proteolysis, featured by significantly deficient ratios of proteolytic destruction of low- and high-molecular proteins (by 38,8% and 17,1% accordingly) and accompanied with simultaneous significant growth (52,1%) of collagenolytic activity of blood plasma. Observed findings perhaps can be explained by the increased level of α2-macroglobulin, which has been shown to inhibit endopeptidases. Consequently, it suppresses the proteolytic destruction of low-molecular proteins in examined patients [6].

Enhanced collagenolysis indicates the augmented activity of collagenase and may be considered as an evidence of accelerated destabilization processes in cerebral atherosclerotic plaques. The presence of instable (or "explosive") plaques is the characteristic trait of diabetic macroangiopathies. The plaque stability depends on the persistence of fibrous coat and is conditioned by the intensity of synthesis and degradation of collagen. The latter is synthesized by means of exchange of fibrin for collagen and realization of macrophage-fibroblast interaction. Elevated propensity for thrombosis, resulted from declined fibrinolysis, and inhibition of proteolytic activity promote imbalance between proteolysis and collagenogenesis, accelerating the latter with subsequent formation of fibrous coat in atherosclerotic plaques [5]. However, under the influence of the tumor necrosis factor-α and interleukine-1, released by macrophages in the infiltration zone, the activity of collagenase is increased, providing collagenolysis and destabilization of plaques [7].

IV. Conclusions.

1. In diabetic patients with chronic impairment of cerebral circulation, proteolytic protein destruction, accompanied with simultaneous activation of collagenolysis, is reported to be inhibited and indicate the intensity of destabilization processes in atherosclerotic plaque.

2. The disorders of proteolytic plasma activity progressed proportionally to the stage of diabetic encephalopathy.

Prospects for further research is to elaborate effective correction mode for the disorders in proteolytic plasma activity in patients with diabetic encephalopathy.

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