Excessive Glycation of Pericapillary Pericytic Matrix Components is an Essential Mechanism of Arterial Hypertension Development in Hyperglycemia

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In patients with essential hypertension, inhibition of glucose utilization in tissues was detected similar to that in diabetics. High levels of glycated compounds were found in cerebral, cardiac, and renal tissues of patients dead from coronary heart disease complicated and not complicated from diabetes mellitus and essential hypertension compared to victims dead from traumas. Experimental studies on rabbits and rats showed that the content of glycoconjugates in tissues did not increase in short-term (exogenous or stress-associated) hyperglycemia, while accumulation of glycoconjugates in pericapillary, pericytic, and cellular structures in long-term hyperglycemia caused deformation of tissue ultrastructure. These disorders can impede capillary transudation, initiate and stabilize arterial hypertension, and lead to multiple organ failure.

Key Words: *hyperglycemia; nonmetabolizable glycoconjugates; inhibited transudation; arterial hypertension; multiple organ failure*

The pericapillary-pericytic space (PPS) connects blood capillaries and tissue cells and mediates the delivery of oxygen, metabolites, signal molecules, *etc.*, to cells with transudation and transport of cytokines, hormones, waste products, *etc.* from cells. Hence, the state of cellular, fibrous, colloid, and other structures in this space is essential for circulatory parenchymatous relationships and functional parameters of tissue. Systems of urgent mobilization (glycogenolysis, gluconeogenesis) and delivery of glucose (circulatory mechanisms) during activation of energy-dependent processes in the cells (cell hyperfunction) appeared in human organism in the course of phylogenies. However, glucose utilization is limited by intracellular mechanisms of its metabolism [8]. Therefore, dyscoordination of glucose delivery/utilization can lead to its accumulation in PPS during some period. This leads to non-enzymatic glycation of proteins, peptides, lipids (glycoproteins, glycolipids, *etc.*) under these conditions. Glycoconjugates (GC) formed during short-term elevation of glucose level in PPS (alimentary hyperglycemia, temporarily limited expenditure) act as a sort of pericytic depot, because they are easily dissociated during the formation of glucose concentration gradient as a result of its utilization by cells. However, if the dyscoordination status lasts for several hours, unstable GC are transformed into more inert Schiff bases and then after several days into nondissociated final glycation products [5]. All GC are extremely hydrophilic, but water in them does not participate in cell trophics; moreover, it causes tissue swelling, impedes transudate access to cells, and disorders their metabolism. This swamping phenomenon (disorders in normal delivery and release of intracellular fluid containing nutrients) was detected in cells adjacent to the necrotic zone in myocardial infarction. In stubborn hyperglycemia, swamping in PPS can impair not only oxygen and substrate delivery to

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the cells, but also mechanisms of Starling equilibrium and lymph circulation [5].

We studied the formation of disorders in the circulation–tissue relations in hyperglycemia and possible contribution of these disorders to the development of arterial hypertension.

MATERIALS AND METHODS

The intensity of glucose consumption by tissues was studied in patients with diabetes mellitus (DM) and essential hypertension compared to normal subjects. GC distribution in brain tissues (hypothalamus), myocardium, and kidneys was studied in subjects dead from myocardial infarction, including those suffering from DM and essential hypertension, in comparison with victims of injuries. The GC levels in the above tissues were measured in rats and rabbits exposed to exogenous short-term and lasting hyperglycemia and under stress conditions.

We failed to find descriptions of methods for direct registration of tissue capacity to utilize glucose *in vivo*. A simple method for quantitative evaluation of glucose utilization by tissues has been developed. The content of glycated compounds in postmortem tissues and in experimental animals was measured by microscopic registration of PAS-positive substances on tissue sections. A short-term (3 days) exogenous hyperglycemia was reproduced in rats by daily intraperitoneal injections of 5 ml 10% glucose solution, long-term (30-32 days) conditions was induced by daily intraperitoneal injections of glucose in volumes increasing every 5 days: from 5 ml 10% solution to 10 ml 15% solution. Stress was induced in rabbits by limited (8×8×8 mm) destruction of the skeletal muscle and immobilization (6 h daily 3 days running) in rats [4]. Glycemia was monitored in animals using the Smart Scan compact system.

The results were statistically processed by routine method of indirect differences between the common arithmetic means and all variants in the studied groups with subsequent evaluation of the significance of the detected differences.

RESULTS

The intensity of glucose consumption by tissues after overnight fasting and before treatment was 24.2±5.6 units in patients (40-60 years; N=11) with DM-1 and DM-2, treated at endocrinology department of regional hospital. In normal subjects of the same age (N=8) this value was 45.5±2.3 units. These data indicate worse glucose consumption in the diabetics (p<0.02). Hourly testing of glycemia level and intensity of glucose consumption by tissues in patients with non-insulin-dependent DM showed reduction of glucose absorption by tissues with increasing glycemia intensity. It seems therefore that hyperglycemia impedes glucose utilization by tissue cells. However, in normal subjects (N=7) with alimentary hyperglycemia (3 h after consumption of 100 g sugar with 200 ml tea after fasting) glucose absorption by tissues did not decrease; moreover, in 4 subjects this parameter somewhat increased. This means that short-term episodes of hyperglycemia in normal subjects do not reduce the intensity of glucose absorption by cells, while in diabetics the increase of hyperglycemia can indicate inhibited glucose absorption by tissues.

Since blood pressure was episodically or constantly high in all diabetics examined, we evaluated the intensity of glucose absorption by tissues in patients with essential hypertension treated at Bobachevskaya Roshcha sanatorium (Tver). Glucose utilization index in these patients (N=15) was 28.65±4.58 units *vs.* 51.27±2.96 units in controls (N=12) (p<0.001). Hence, glucose utilization by tissues was reduced (similarly as in DM patients) in patients with manifest hypertension without signs of DM or with a history of blurred signs of DM.

Low utilization of glucose by tissues in DM patients could be caused by various factors, including PPS swamping because of glycated compounds. It was therefore interesting to compare the levels of these compounds in PPS of dead subjects with and without history of DM. The levels of glycated (PAS-positive) substances were measured in the brain, heart, and kidneys of men dead from coronary disease (N=8),

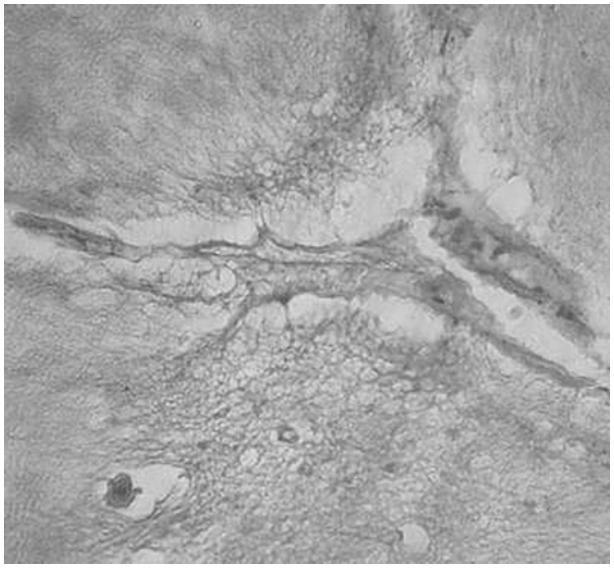

Fig. 1. Brain tissues. Accumulation of GC in tissue, vascular, and other structures, capillary and tissue disorganization resultant from a drastic increase in the content of pericapillary and pericytic fluid. Here and in Figs. 2 and 3: PAS reaction. ×40.

who had suffered from hypertension (*N*=5) or DM complicated by hypertension (*N*=3) in comparison with victims of injuries (*N*=3). The levels of glycated compounds in all analyzed tissues were higher in all cases of coronary death in comparison with the levels in victims of injuries, particularly in membrane and perivascular pericytic structures. In the brain (Fig. 1), the highest concentrations of PAS-positive compounds were found in capillary lumens and walls. Numerous vacuoles formed by slightly stained, seemingly gelatinous fluid, were seen in the longitudinal sections of vessels in the lumens and perivascular spaces. Stretched fine threads between the vessels and adjacent tissues were seen in this fluid in some places; this indicated high pressure of perivascular fluid on the brain vessels and cells. Numerous PAS-positive compounds were found in the pericytic spaces.

Vascular and tissue relations similar to those found in the brain were seen in heart tissues (Fig. 2). The content of PAS-positive compounds was also high in the endocardium, cardiomyocyte nuclei and sarcolemmas. Sharp dissociation of cardiomyocytes by pericytic fluid was seen in some regions of the myocardium.

The kidneys play the key role in elimination of hyperglycemia, and presumably that is why particularly high concentrations of glycated compounds and obvious consequences of their accumulation in tissue structures were detected in this organ (Fig. 3). The tubular lumens in an appreciable portion of the nephrons were filled by destroyed PAS-positive mass, no lumens were detectable, the capsules of the glomerular system were stretched and damaged, capillaries were deformed and in some nephrons partially or completely destroyed.

Hence, the development of life-threatening (including hypoxic) injuries in tissues of victims of coronary death could be caused by accumulation of pericytic GC irrespective of the presence or absence of the diabetic syndrome. This was confirmed by the results of experiments on animals with experimental hyperglycemia (but not DM).

The content of GC in PPS did not increase in the analyzed tissues (brain, myocardium, kidney) of rats with short-term (3 days) hyperglycemia caused by immobilization stress (*n*=5) or glucose injection (*n*=5) or in the tissues of rabbits (*n*=5) on day 3 after muscle injury. However, we observed high adhesion of blood cells in these animals resulting from more intense formation of the glycocalyx, this indicating activation of intracellular enzyme-dependent glucose utilization by cells.

The pattern of GC accumulation in PPS in the studied tissues of rats (*n*=5) in lasting high hyperglycemia was similar to that in humans dead from coronary

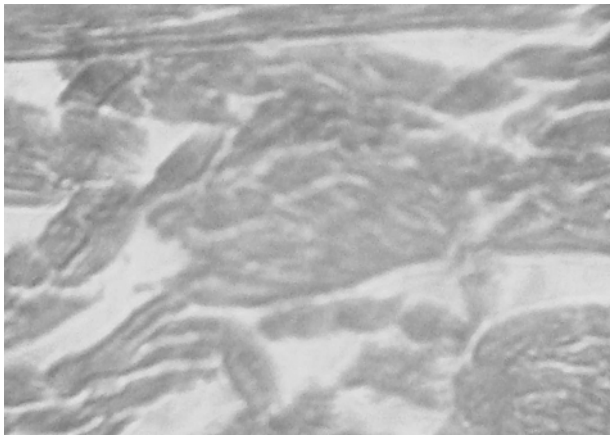

Fig. 2. Myocardial tissues. Accumulation of GC in myocardial structures, pronounced separation of cardiomyocytes with pericytic fluid.

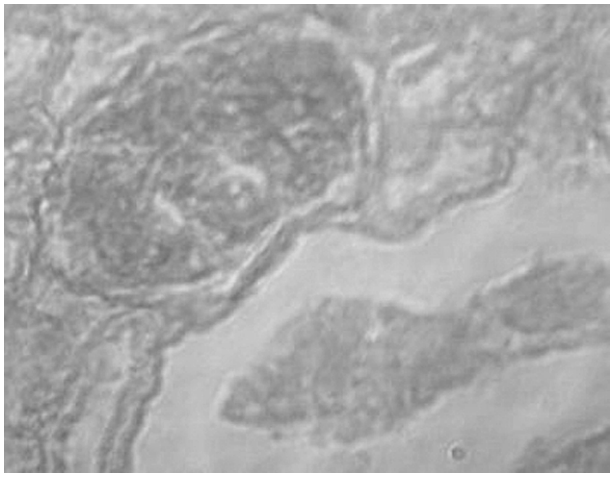

Fig. 3. Renal tissues. High concentrations of GC, deformation and destruction of glomerular, tubular, and capillary structures.

disease. Presumably, overall augmenting swamping of the pericytic space inevitably impedes transudation and promotes the formation of a volumic mechanism of arterial hypertension [7]. Oxygen and metabolite insufficiency in the regulatory regions (for example, in the hypothalamus and kidneys) augmenting during this process can stimulate the mechanisms of circulatory perfusion and stabilize arterial hypertension.

Hence, diabetic and nondiabetic but lasting hyperglycemia seems to be associated with accumulation of stable GC in the perivascular pericytic space [9]; these complexes inhibit capillary transudation and promote the formation of volume hypertension. As this swamping also involves the regulatory centers (hypothalamus, kidneys, *etc.*), their augmenting oxygen and metabolite starvation can result in stimulation of the hemodynamic systems, increasing the tissue perfusion and stabilizing the hypertension, which with time can be complicated by vascular disorders, multiple organ diseases, and early aging [1,3,6]. It seems that this circumstances are responsible for glucose tolerance

disorders found in almost 50% patients with hypertension [2]. Hence, early detection of glucose tolerance disorders can help to prevent the development of arterial hypertension and early aging caused by multiple organ pathologies in subjects liable to hyperglycemia.

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