TIME COURSE OF GLYCOSYLATED HEMOGLOBIN AND MALONIC DIALDEHYDE IN EXPERIMENTAL DIABETES

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Glycosylated hemoglobin (HbA_{1c}) is one of the minor fractions of hemoglobin A, and is a product of nonenzymic post-translation combination of glucose with globin, with the formation of a Schiff base and subsequent Amadori transformation. The glycosylation process depends primarily on the blood sugar level, and this is the reason why it is important to determine HbA_{1c} in diabetes as an integral parameter of disturbed glucose hemostasis over a period of the last 1-3 months. Besides the value of HbA_{1c} as a diagnostic criterion, which is reflected in a large number of publications [2, 5, 6], it also bears definite responsibility for metabolic changes and for the oxygen transport function. Potentiation of glycosylation of hemoglobin in diabetes embodies an increase in the affinity of hemoglobin for oxygen, venous hyperoxia, reduced utilization of oxygen by the tissues, and tissue hypoxia [5]. We also know that one of the mechanisms of destruction of biological membranes is the process of lipid peroxidation (LPO) – an oxygen-dependent process taking place under physiological conditions and activated by disturbance of the oxygen balance in the tissues: in the presence either of an excessive oxygen concentration or oxygen-deficiency states [3, 4]. Intensification of LPO is observed in diabetes [8, 9], although the connection between the two processes, namely LPO and glycosylation of hemoglobin, in the early stages of diabetes has not been studied.

The aim of this investigation was to study levels of HbA_{1c} and the LPO product – malonic dialdehyde (MDA), in the course of experimental diabetes.

EXPERIMENTAL METHODS

Experiments were carried out on 11 dogs of both sexes weighing 12-18 kg. Before the operation the animals were deprived of food for 1 day. Diabetes was induced by the method described previously [1], by resection of 70% of the pancreas, accompanied by injection of 250 mg alloxan into the superior pancreaticoduodenal artery. Blood samples for determination of sugar, HbA_{1c}, and MDA were taken from a subcutaneous vein of the hind limb before the operation and 1, 3, 5, 7, 14, 21, 28, 45, and 60 days thereafter. The fasting blood sugar was determined by the orthotoluidine method with a standard kit of reagents. The end product of LPO, namely MDA, was determined by the test with thiobarbituric acid [7]. Blood for determination of HbA_{1c} was collected into test tubes with citrate in the ratio of blood-citrate = 1:1, and a modified method of isoelectric focusing in PAG plates was subsequently used [2]. Insulin was determined by a radioisotope method using the standard "Rio-INS-PG^{125}" kit before the operation on the 28th and 60th days thereafter.

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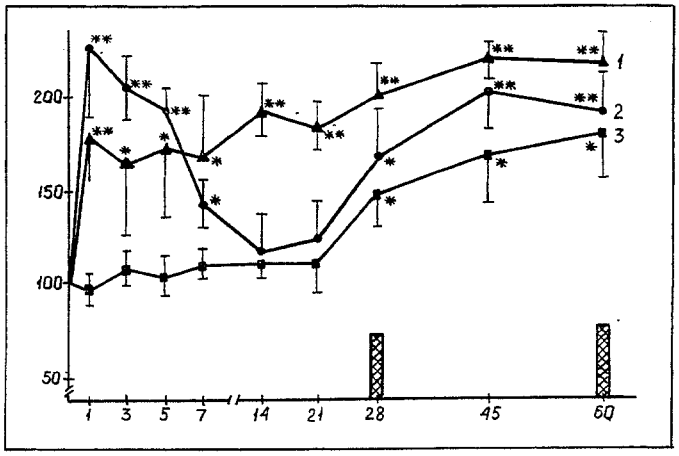

Fig. 1. Changes in blood sugar, MDA, HbA_{1c}, and insulin levels of dogs with experimental diabetes (M ± m, %) 1) Sugar, 2) MDA, 3) HbA_{1c}; 4) insulin. *p < 0.05, **p < 0.02. Values for intact dogs before operation taken as 100%.

EXPERIMENTAL RESULTS

The time course of blood HbA_{1c}, MDA, and sugar levels of dogs with diabetes is illustrated in Fig. 1.

The blood HbA_{1c} level in intact animals was 6.4 ± 0.32%; values for HbA_{1c} remained within normal limits during the first 3 weeks after the operation, when the blood sugar level was significantly above the initial value. Starting with the 4th week the HbA_{1c} concentration rose significantly (by 54%) and still remained high 2 months after the operation, when it was 183% of its initial value.

The MDA level was sharply elevated with effect from the 1st day after the operation (by 130%); later it fell a little, although it remained above the initial values for 1 week. The MDA level after 2-3 weeks was the same as initially, but starting with the 4th week and until 2 months of observation it was increased.

Hyperglycemia occurred throughout the postoperative period of observation.

The insulin concentration on the 28th and 60th days was depressed, at 74% ($p < 0.05$) and 78% of the initial value.

Determination of correlation between the HbA_{1c} and sugar concentrations and also between HbA_{1c} and MDA revealed moderately strong positive correlation in the first case ($r = 0.67$) and no correlation in the second ($r = 0.29$).

The absence of correlation between HbA_{1c} and MDA can be explained by analysis of the curve of the change in MDA. A definite contribution to the increase in MDA concentration immediately after the operation was made by alloxan, the mechanism of action of which is explained by the majority by the free-radical hypothesis [8], and the subsequent fall of MDA can be regarded as a compensatory reaction due to partial restoration of functional activity of the alloxan-damaged β-cells. The rise of HbA_{1c} from the 4th week led to disturbance of the oxygen-transport function of the blood and tissue oxygen balance, and the possibility cannot be ruled out that the second MDA peak was due to an increase in the partial pressure of oxygen in the venous blood, increasing tissue hypoxia, and induction of free-radical lipid oxidation. The fall in the blood level of insulin, which is known to be involved in the metabolism of lipid peroxides [9], which was found promotes accumulation of toxic LPO products and further progression of the disturbances of cell metabolism in diabetes.

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TROPAPHEN IN THE EXPERIMENTAL PHARMACOTHERAPY OF COR PULMONALE

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Peripheral vasodilators (PV) are nowadays widely used in clinical practice to treat heart failure because of their ability to improve cardiac activity indirectly through a change in tone and filling of the peripheral vessels and reduction of the pre-load and/or post-load on the heart. Reports of the use of PV with different mechanisms of action, including myotropic agents, calcium antagonists, and inhibitors of angiotensin-converting enzyme, in heart failure have been published [4, 9, 15]. The role of α-adrenoblockers (α-AB) in this aspect is unclear and calls for intensive study.

The aim of this investigation was to study the effect of the unselective α-AB tropaphen* on the cardio- and hemodynamics in a form of heart failure refractory to glycoside therapy, namely experimental cor pulmonale (CP), associated with chronic nonspecific lung diseases (CNLD).

EXPERIMENTAL METHOD

Experiments were carried out on 36 mongrel dogs of both sexes weighing 16-25 kg. The experiment consisted of three series: I) control animals; II) animals with a model of CP due to pulmonary hypertension (PHT), associa-

*Tropine ester of β-acetoxyphenyl-α-phenylpropionic acid.

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