CHANGES IN FUNCTION AND ENERGY METABOLISM OF THE MYOCARDIUM IN DOGS WITH EXPERIMENTAL DIABETES

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KEY WORDS: diabetes mellitus; heart; myocardial metabolism; coronary circulation; acid-base balance.

Cardiovascular complications are among the principal pathological manifestations of diabetes [3]. Primary metabolic disturbances arising in the early stages of development of diabetes, when no significant structural lesions have yet developed in the coronary vessels and myocardium, may be of essential importance in the pathogenesis of myocardial lesions [1, 7, 8].

The aim of this investigation was to study relations between the magnitude and direction of disturbances of the functional state of the heart and coronary circulation and the characteristics of changes in the principal parameters of myocardial energy metabolism during the development of experimental diabetes mellitus.

EXPERIMENTAL METHOD

Experiments were carried out on 44 mongrel dogs of both sexes weighing 6-25 kg. Experimental diabetes was produced in 24 dogs by a single intravenous injection of a 5% aqueous solution of alloxan (75 mg/kg). Functions of the heart and coronary circulation and myocardial metabolism were investigated in the dogs 1-2 months after receiving alloxan. Catheterization, extracorporeal programmed perfusion, and resistography of the coronary vessels were carried out on animals with an intact chest [2], and catheterization and drainage of the coronary sinus, with the taking of blood samples for biochemical tests and gas analysis, and catheterization of the chambers of the heart and of the great vessels were undertaken under morphine–chloralose anesthesia (2.5 and 50-100 mg/kg respectively). Parameters of the cardio- and hemodynamics and the ECG were recorded on the Mingograf-81 polygraph and the 6NEK-401 instrument, and the acid-base balance and gas composition of the blood were determined by means of a Corning-166 instrument. The cardiac output was determined by the thermodilution method. In arterial blood and blood draining from the heart glucose was determined by the o-toluidine method, pyruvic acid by the reaction with 2,4-dinitrophenylhydrazine [4], lactic acid by the method in [5], nonesterified fatty acids (NEFA) by the method in [6], and ketone bodies by the method in [4].

EXPERIMENTAL RESULTS

In animals with a low (under 5.2 ± 0.24 mmoles/liter) and moderate (up to 9.3 ± 0.44 mmoles/liter) level of hyperglycemia the values of most parameters of cardiac output and contractile function did not differ significantly from normal. Marked disturbances of circulatory function were found in animals whose blood glucose level was raised more than threefold (on average from 4.11 ± 0.16 to 15.4 ± 0.88 mmoles/liter). They were manifested as a fall in the cardiac index and working index of the left ventricle, a reduction of the maximal rate of contraction of the left ventrical by 24% (from 377 ± 55.91 to 287.9 ± 14.10 kPa/sec; $p < 0.01$), and also an increase in the period of tension by 0.020 ± 0.006% and the myocardial tension index by 11.38 ± 2.81%, and by a decrease in the ejection time by 0.020 ± 0.004%, in the mechanical coefficient by 0.996 ± 0.253%, and in the intrasystolic index by 10.62 ± 1.64% compared with the expected values. The volume of the perfusion flow in the

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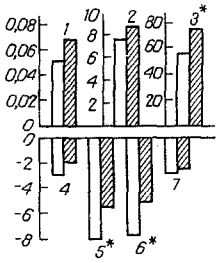

Fig. 1

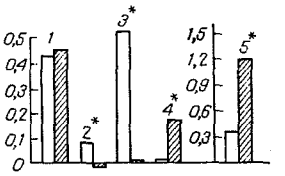

Fig. 2

Fig. 1. Changes in difference between parameters of acid-base balance and gaseous composition of blood entering and leaving the heart (coronary arteriovenous difference) in dogs with severe alloxan diabetes. 1) pH; 2) pO_2 (in kPa); 3) blood oxygen saturation (in %); 4) pCO_2 (in kPa); 5) CO_2 (in mmoles/liter); 6) HCO_3^- (in mmoles/liter); 7) BE (in mmoles/liter). Unshaded columns) control; shaded columns) alloxan diabetes. Asterisks indicate $p < 0.05$.

Fig. 2. Changes in difference between concentrations (in mmoles/liter) of some energy-yielding substrates in blood entering and leaving the heart (coronary arteriovenous difference) in dogs with severe alloxan diabetes. 1) Glucose; 2) pyruvic acid; 3) lactic acid; 4) ketone bodies; 5) NEFA. Remainder of legend as to Fig. 1.

territory of the circumflex branch of the left coronary artery was 31% less than in the control (38.0 ± 7.7 and 56.0 ± 2.6 ml/min respectively). In animals with marked hyperglycemia the myocardial oxygen consumption, estimated from the product of the arterial pressure and the heart rate, and also from the coronary arteriovenous oxygen difference (Fig. 1), was the same as in healthy animals, or increased.

In healthy animals the myocardium utilized glucose, lactic, and pyruvic acids, and NEFA. The coronary arteriovenous difference for these substrates was 0.43 ± 0.055, 0.52 ± 0.067, 0.083 ± 0.0072, and 0.33 ± 0.040 mmoles/liter respectively, so that relative to the glucose level in their arterial blood (up to 15.4 ± 0.88 mmoles/liter), to the fall in pH (to 7.242 ± 0.037), and to the buffer base (BE) level (to −13.1 ± 1.55 mmoles/liter), extraction of glucose by the myocardium was virtually unchanged, although it was only 2.9% of glucose concentration in the arterial blood. Unlike in healthy animals, in those with experimental diabetes not only did the heart not utilize lactic acid, but in many experiments it secreted pyruvic acid into the coronary sinus (Fig. 2). Since the concentrations of these substrates in blood flowing into the heart in healthy and diabetic animals did not differ significantly, the reduction of their utilization by the myocardium of the animals with diabetes indicates limitation of the utilization of glucose and of its metabolites as energy-yielding substrates. Meanwhile, in connection with elevation of the concentrations of NEFA (from 1.19 ± 0.10 to 3.42 ± 0.50 mmoles/liter) and of ketone bodies (from 0.08 ± 0.052 to 0.84 ± 0.21 mmoles/liter) in the arterial blood, an increase in their utilization by 4 and 40 times respectively was observed. This restructuring of the energy supply to the myocardium was accompanied by an increase in the myocardial oxygen consumption and an increase in the coronary arteriovenous difference with respect to oxygen from 55.6 ± 1.74 to 73.1 ± 1.10% ($p < 0.001$), and also by a decrease in CO_2 secretion into the coronary sinus and a decrease in the coronary arteriovenous difference for CO_2 from −8.1 ± 1.02 to −5.3 ± 6.74 mmoles/liter ($p < 0.01$).

As a result of the rise of the level of oxygen consumption (on average by 24%; $p < 0.001$) during diabetes the functional reserve of the heart, estimated by the degree of increase in consumption of substrates and oxygen during adrenergic stimulation of the heart, was reduced. Thus after injection of 5 μg adrenalin into the coronary perfusion system the decrease in the coronary arteriovenous difference for pO_2 and the blood oxygen saturation in the coronary sinus were significantly smaller than in the control (0.21 ± 0.03 and 0.35 ± 0.05 kPa; $p < 0.001$ and 0.41 ± 0.06 and 0.69 ± 0.11%; $p < 0.001$ respectively).

The certain degree of limitation of the blood supply to the heart in diabetes is probably partially compensated by increased extraction of oxygen by the myocardium. Limitation of the utilization of metabolic glucose can be explained by an increase in the contribution of NEFA and ketone bodies to myocardial energy metabolism.

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DEVELOPMENT OF DIABETES MELLITUS IN THE OFFSPRING OF FEMALE RATS WITH ALLOXAN DIABETES IN SIX GENERATIONS

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Some of the first-generation offspring of female Wistar rats with alloxan diabetes, mated with healthy males, developed latent or manifest diabetes mellitus, which was either transient or permanent [1]. Meanwhile in the presence of frank alloxan diabetes in males and in the absence of diabetes in females, none of the first generation offspring developed diabetes mellitus [2]. Delay of the utilization of parenterally administered glucose, increasing in each successive generation, is observed in the offspring of three generations of rats with subclinical alloxan diabetes, associated with normoglycemia and aglycosuria [4]. The same investigators showed later a progressive disturbance of glucose tolerance in the 2nd-7th generations, reaching the stage of manifest diabetes mellitus in the 7th generation with a blood glucose level, after fasting for 16 h, of 1.32 ± 2.8 mg% in females and 1.38 ± 3.2 mg% in males [5].

This paper describes the study of the development of diabetes mellitus in the offspring of female Wistar rats with alloxan diabetes in six generations.

EXPERIMENTAL METHOD

Female rats (probands) were given alloxan at the age of 1 month by subcutaneous injection of a dose of 180-200 mg/kg. Six rats which developed permanent frank alloxan diabetes, with a glucose level of 12.1-21.1 mmoles/liter after fasting for 16 h, were used in the experiments. The blood sugar was determined by the method of Somogyi and Nelson. The morning blood sugar after fasting for 16 h was determined every 7-14 days. Female rats with alloxan diabetes were mated at the age of 3-4 months with healthy males which had received no alloxan. The glucose tolerance test (GTT) was studied in the offspring of six generations (346 rats) by injecting glucose into the stomach through a tube in a dose of 400 mg/kg at the end of the 1st, 2nd, 3rd, 4th, 5th, and 6th months of postnatal life. The offspring of rats with

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