erythrocytes. It will be clear from Table 1 that the velocity of Na^+/H^+ exchange in the erythrocytes of young rats (age 4 weeks) was approximately doubled, and in SHR erythrocytes this increase was reduced by 20%.

It can be tentatively suggested that differences in the maximal velocity of Na^+/H^+ exchange observed in erythrocytes of young SHR, in the prehypertensive stage, are due to differences in cytoskeleton formation. In fact, it has been shown on chick embryonic erythrocytes that the ratio of the content of protein in the 4.1 band to spectrin increases in the course of development from 0.83 to 3.64 [13]. Differences in the properties of the erythrocytes of young SHR and WKY rats were seen most clearly in the experiment whose results are given in Fig. 3: incubation of the erythrocytes of rats aged 16 weeks for 4 h in the presence of orthovanadate led to very slight hemolysis of the cells, recorded as hemoglobin release (Fig. 3: 1, 2). No differences were found between SHR and WKY rats in this age group. Erythrocytes of young rats (especially SHR) were much more sensitive to the action of orthovanadate: under these same conditions, after incubation for 4 h, 95% and 37%, respectively, of their hemoglobin was released from SHR and WKY erythrocytes (Fig. 3: 3, 4).

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EFFECT OF 1-(CHLOROMETHYL)-SILATRANE ON CHANGES IN BLOOD CELLS DURING THE EXTRACORPOREAL CIRCULATION

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UDC 616.12-089.166:616.12-78/-06:616.155.18-085.246.4:547.245

KEY WORDS: extracorporeal circulation; assisted circulation apparatus; hemolysis; lipid peroxidation; 1-(chloromethyl)-silatrane.

The creation and use of assisted circulation apparatuses (ACA) during operations on the heart, the use of an assisted circulation for the treatment of heart failure, and also the fitting of artificial heart valves and artificial main blood vessels are all connected with the problem of trauma to blood cells (BC) [3, 10-12]. Injury to and destruction of erythrocytes (hemolysis) and other BC are the main obstacles to the long-term use of assisted circulation methods and they greatly complicate the process of postoperative rehabilitation of patients. The most important traumatic factors include the effect of a foreign surface, mechanical trauma, the velocity and duration of perfusion, and oxygenation [1, 3, 12, 14]. Stabilization of the integrity and functional activity of BC during the extracorporeal circulation (ECC) is thus an acute problem which faces modern cardiology. In clinical practice no

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Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 104, No. 10, pp. 418-420, October, 1987. Original article submitted January 12, 1987.

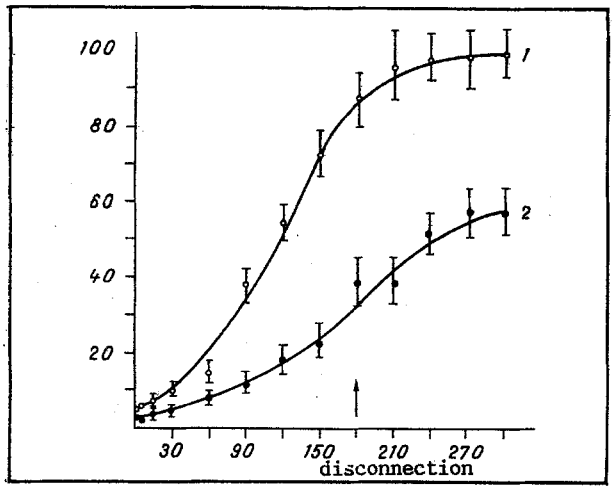

Fig. 1. Changes in extraerythrocytic hemoglobin level with time in control (1) and with administration of CMS (2). Abscissa, duration of work of ACA (in min); ordinate, plasma hemoglobin concentration (in mg%). Here and in Figs. 2 and 3, arrow indicates disconnection of ACA.

measures are yet available for the correction of this biological damage, although there is no doubt about the urgency of the search for compounds which would increase the resistance of BC to the action of ECC. However, very little research has yet been done on this problem [1, 12]. The writers showed previously that 1-(chloromethyl)-silatrane (CMS) effectively protects membranes of BC when exposed to the action of ultrasound, or when undergoing changes as a result of perfusion (roller pump) [9], the action of HCl and other disintegrating agents [6], and under conditions of immobilization stress [4, 5], and it exhibits antioxidant properties [8].

The aim of this investigation was to determine the prospects for the use of CMS as a protector of BC during the ECC.

EXPERIMENTAL METHOD

Experiments were carried out on dogs. CMS was injected intravenously in a dose of 1 mg/kg in 10 ml of physiological saline. In the control, the equivalent volume of physiological saline was injected. After 1 h the femoral vein was dissected in the animals and the ACA filled with blood through a cannula. The AIK-5 apparatus was used (temperature 37°C, power 40 strokes/min, circulating blood volume 40 ml/stroke, oxygen consumption 1 liter/min). The ACA functioned on a closed circuit mode for 3 h, and blood samples were taken for analysis after 30 sec, 15 and 30 min, and thereafter every 30 min for 2 h. To study the action of ACA on the integrity and functional activity of BC, the plasma hemoglobin (Hb) concentration was determined [7], the kinetics of lipid peroxidation (LPO) was determined in the blood serum by measurement of chemiluminescence (ChL) [2], and the ultrasonic resistance of the erythrocytes (URE) was demonstrated [13].

EXPERIMENTAL RESULTS

ACA under ECC conditions is a powerful pain-inducing factor, possessing a complex disintegrating action. It will be clear from Fig. 1 that the Hb level began to rise significantly after 30 min, and remained constant when the ACA was disconnected. URE in the first 120 min fell appreciably, and increased when the ACA was disconnected (Fig. 2). However, the changes in LPO kinetics with time deserve the closest attention. As will be clear from Fig. 3, in the first 15 min of work of the ACA marked activation of LPO took place, followed by inhibition with respect to all parameters of ChL. With respect to some parameters of ChL, a second wave of activation of the process was observed at different time intervals, and was evidently connected either with the critical concentration of heme iron or with a fall in the level of antioxidants in the blood.

The use of CMS in the concentration specified (Figs. 1-3) had a marked protective action. The silatrane reduced the rate of Hb outflow into the blood plasma, and increased the resistance of the membranes to ultrasound; throughout the experiment, URE remained at its

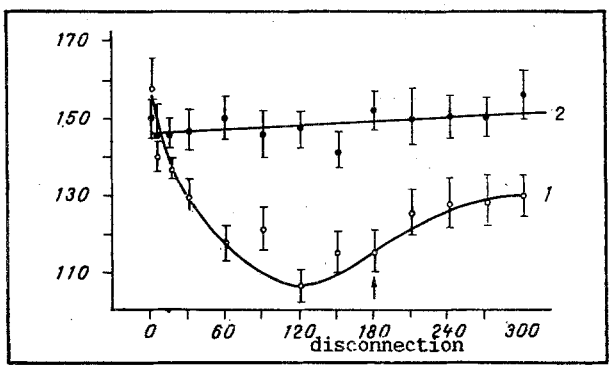

Fig. 2. Kinetics of changes in URE in control (1) and after use of CMS (2). Abscissa, duration of work of ACA (in min); ordinate, 50% hemolysis time (in sec). Ultrasound source was the UZT-101 therapeutic apparatus with IUT-0.3-88-3 generator, frequency 880 kHz, power 0.6 W/cm^2, on the continuous mode.

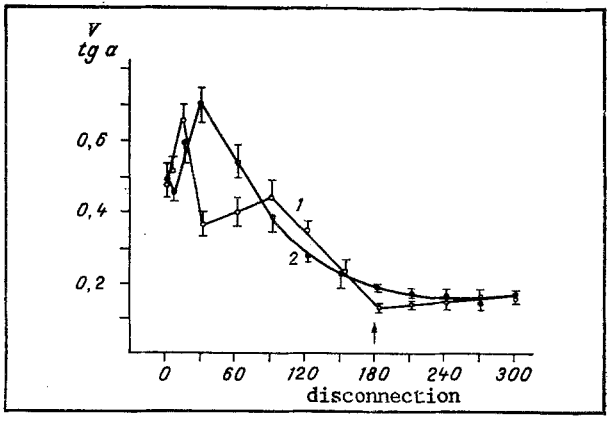

Fig. 3. Effect of CMS (2) on kinetics of LPO (1 — control). Abscissa, duration of work of ACA (in min); ordinate, rate of development of slow chemiluminescence flash (V).

initial level. A particularly important feature is that CMS reduced activation of LPO during the first 15 min and maintained it at its initial level for a certain length of time.

Appreciable changes in the kinetics of LPO during the first minutes of work of ACA, when virtually no hemolysis of erythrocytes could be detected, is evidence that activation of LPO precedes direct destruction of erythrocytes and of other BC.

The process of hemolysis began with activation of LPO, which led ultimately to stabilization of the erythrocyte membranes and to outflow of hemoglobin into the plasma. It may be that initially (in low concentrations) hemoglobin activates LPO (the second wave of activation of the process), but after accumulating, on the contrary, it inhibits LPO, as has also been shown for Fe^{++} ions [2].

The results are thus evidence that CMS, in a concentration of 1 mg/kg, increases the resistance of membranes of BC of animals to the damaging action of ACA. Stabilization of the structure and functions of BC is based on the ability of CMS to regulate the intensity of LPO processes in biological membranes. These results may be important for the use of CMS as a stabilizer of BC under ECC conditions.

The authors are grateful to E. Ya. Kaplan and V. S. Gigari for help with the work and for useful discussion of the results.

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ENDOCRINE DISTURBANCES IN THE EARLY STAGES OF DEVELOPMENT OF EXPERIMENTAL CHRONIC PANCREATITIS

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UDC 616.37-002.2-036.4-07:616.379-008.6/-092.9

KEY WORDS: pancreas; insulin; glucagon; chronic pancreatitis; diabetes mellitus.

Information on hormonal activity of the pancreas and the character of changes in carbohydrate tolerance in chronic pancreatitis is inadequate and contradictory. The urgency of this problem is due to the difficulty of diagnosis and treatment of this disease and the possibility of development of profound endocrine disturbances, culminating in diabetes mellitus [1].

In diabetes insulin secretion is reduced, as shown by a decrease in insulin release in response to glucose intake, which may be associated with damage to the receptor for this carbohydrate or a defect in the nervous or metabolic chain of insulin release [6, 8].

A comparative study of the secretion of insulin and glucagon [13] alters the traditional idea of diabetes mellitus. It was suggested that changes in glucagon secretion also play an important role in the development of severe diabetic hyperglycemia, for it is the principal regulator of glucose release by the liver, through activation of glycogenolysis and gluconeogenesis, inhibition of glycogen synthesis, and changes in glucokinase activity [9], i.e., it has an action opposite to that of insulin. The normal response of the A cells is characterized by reduced glucagon production in response to hyperglycemia; insulin plays a role in the penetration of glucose into these cells [13]. The molar ratio of the two hormones may provide an indicator of the direction of metabolism [14] and it is the principal factor affecting the glucose level. Under normal conditions this index varies from 0.4 to 70 [5]. According to data in the literature [10] no increase in the molar ratio of the hormones was found in diabetics after taking food, and the degree of these disturbances, moreover, corresponds to the severity of the clinical state. There is little information regarding changes in this parameter under normal conditions or in diabetes. Even less has been written about the

Department of Operative Surgery and Topographic Anatomy, N. I. Pirogov Second Moscow Medical Institute. Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 104, No. 10, pp. 420-423, October, 1987. Original article submitted November 22, 1986.

 0007-4888/87/0010-1370$12.50