ACTION OF STREPTOKINASE ON PARAMETERS OF HEMOSTASIS IN RABBITS WITH TOXIC LIVER DAMAGE DUE TO CARBON TETRACHLORIDE

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Preparations of streptokinase (SK), a protein plasminogen activator secreted by β-hemolytic streptococci, are widely used for the treatment of thrombotic complications. However, problems associated with the use of these preparations in certain internal diseases have not yet been completely solved [10]. Experimental studies of thrombolytic preparations are carried out as a rule on intact animals, and this imposes certain limitations of the results [6].

Considering the role of the liver in the regulation of fibrinolysis [1], the pharmacokinetics of SK preparations [13], and also the possibility of onset of states of thrombophilic type and, in particular, of disseminated intravascular clotting in diseases of the liver [12], the aim of the present investigation was to study the specific nature of changes in the parameters of hemostasis in rabbits with experimental toxic liver damage.

EXPERIMENTAL METHOD

Experiments were carried out on 24 rabbits weighing 2.5-3 kg (10 rabbits in the control group, 14 in the experimental). Toxic liver damage was induced by three injections, at intervals of 2 days, of an 80% emulsion of carbon tetrachloride in a dose of 0.16 ml/kg body weight intraperitoneally into the animals of the experimental group [3, 7]. The animals were used to study the parameters of hemostasis 2 days after the last injection. SK (Celiase, Awelysin) was injected intravenously into the rabbits of both groups in a single dose of 60,000 IU/kg body weight in isotonic NaCl solution. Before injection of the SK and 10, 30, 60, and 90 min thereafter, blood was taken from the jugular vein and the thrombin time [2], antithrombin III (by Abildgaard's method), fibrinogen concentration and fibrinolytic activity of the blood plasma (after Lazar), lysis of whole blood clot (afrer Fernlee), and total antiplasmins [8] were determined. The results were subjected to statistical analysis [9].

During the period of the experiment the animals were kept under intravenous thiopental anesthesia (30 mg/kg), and after the end of the investigation they were killed by injection of air into the jugular vein.

Pieces of rabbit liver were fixed in 10% neutral formalin and histological sections were stained with hematoxylin and eosin and with Sudan III.

EXPERIMENTAL RESULTS

After injection of carbon tetrachloride all the animals of the experimental group showed loss of activity, apathy, and refusal to eat — features observed during the development of experimental toxic liver damage [3].

In accordance with the character of the morphological changes discovered in the renal parenchyma the rabbits of the experimental group can be divided into two subgroups. Changes in the parenchyma of the eight rabbits of subgroup 1 were characterized by fatty infiltration, local hydropic dystrophy, signs of karyopycnosis and karyorrhexis, slight edema of the Disse's spaces, and microfocal infiltration with round cells, i.e., the changes were predominantly dystrophic in character. In the six rabbits of group 2 changes in the liver parenchyma were characterized by hydropic dystrophy, signs of cytokaryopycnosis, destruction of the trabeculae, marked edema of the Disse's spaces, disturbances of the hemodynamics, hemorrhages, hyperemia,

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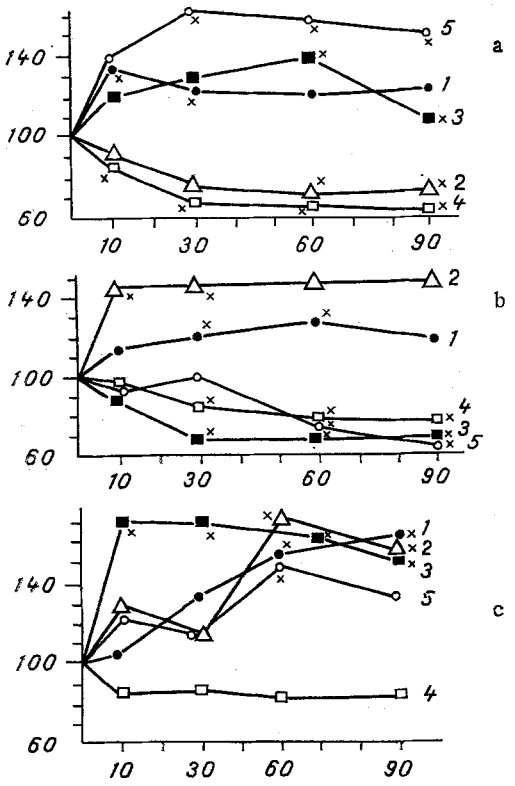

Fig. 1. Dynamics of thrombin time (1), levels of antithrombin III (2), total antiplasmins (3), and fibrinogen (4), and fibrinolytic activity of plasma (5) after injection of SK into intact rabbits (a) and rabbits with toxic liver damage of dystrophic (b) or cirrhotic (c) character. Abscissa, time (in min). Data expressed as percentages of initial values, taken as 100. *P < 0.05 compared with initial value.

proliferation of fibroblastic and histiocytic lymphoid cells, and in individual cases, by accumulation of a yellowish-brown pigment, not staining by Perls' method. Changes in the liver of the rabbits of this subgroup were thus those of the productive type of inflammation (initial stage of cirrhosis).

For the reasons given above, subgroups 1 and 2 will henceforward be examined separately.

Injection of SK in a dose of 60,000 IU/kg body weight into rabbits of the control group caused changes in the parameters studied that are typical [5] of SK preparations: marked acceleration of lysis of the blood clot (to 112 sec, initially over 24 h), increased fibrinolytic activity and thrombin time, lowered level of fibrinogen and antithrombin III (Fig. 1). These changes were observed for 90 min after injection of SK. In response to intensification of fibrinolysis, total antiplasmin activity increased in the blood plasma until the 90th minute after injection.

In the animals of subgroup 1 injection of SK inhibited fibrinolytic activity instead of increasing it. Meanwhile short-term (for not more than 60 min) acceleration of lysis of the whole blood clot was observed, and starting from the 30th minute there was an increasing fall in the fibrinogen level and antiplasmin activity. For 90 min after injection of SK there was a tendency for the thrombin time to lengthen and the antithrombin III level to rise.

Injection of SK into the rabbits of subgroup 2 caused an increase in fibrinolytic activity of the blood plasma, acceleration of lysis of the whole blood clot (to 112 sec, initially over 24 h), and an increase in total antiplasmin activity and lengthening of the thrombin time By contrast with the control, however, the fibrinogen concentration showed little change after injection of SK, but the antithrombin III level rose.

In cases of liver damage described above, the responses of the hemostasis system to administration of SK, an exogenous activator of fibrinolysis, thus changed significantly. During

changes of dystrophic type, activation of fibrinogenolysis and not of fibrinolysis may perhaps have taken place, with the result that the fibrinogen concentration fell (leading to the formation of imperfect fibrin clots and, as a result, to intensification of lysis of blood clots), but the fibrinolytic activity of the plasma did not rise. It can be tentatively suggested that changes of this kind in the substrate specificity of plasmin are connected with redistribution of, for example, antiplasmins. Changes of substrate specificity were recorded previously [4] in relation to the plasmin–α_2-macroglobulin complex. This is confirmed to some extent by the fact that in liver damage of inflammatory type (subgroup 2) an increase in the fibrinolytic activity of the plasma does not lead to a fall in the fibrinogen concentration. One other circumstance should be noted. Whereas in the normal state of the organism the mechanism of fibrin formation are in dynamic equilibrium with the mechanisms preventing fibrin formation, it can be postulated that loading with exogenous plasminogen activator not only leads to destruction of the fibrin formed, but also creates opticals in the way of fibrin formation. The results described above show that this situation was most clearly exhibited in liver damage of the inflammatory type (subgroup 2), when the thrombin time was increased and the antithrombin III level also was raised.

Meanwhile, in the control animals, the antithrombin III level was lowered although the direction of the change in the remaining parameters was identical in rabbits of the control group and of subgroup 2. Consequently, obstacles to a rise of the antithrombin III level appeared in the intact animals in response to injection of SK.

Since not all the changes observed can be explained by intensification of fibrinolysis during activation of plasminogen by SK, it can be tentatively suggested that this is not the only pathway for the action of SK on the body.

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