FIBRINOLYTIC ACTIVITY OF THE BLOOD DURING TRANSIENT CORONARY INSUFFICIENCY IN RATS

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Local transient coronary insufficiency (TCI) with a varied duration of the period of myocardial ischemia (MI), reproducible in animals, is an experimental model of various forms of ischemic heart disease in man: angina, the intermediate coronary syndrome, and states following surgical (for example, aortocoronary bypass) or drug-induced (for example, thrombolysis) revascularization of the myocardium in the acute period of infarction [3-5]. The writers previously discovered significant changes in activity of the clotting and fibrinolytic systems of the blood not only in the ischemic, but also in the reperfusion period of TCI [4]. Disturbances in the hemostasis system under these circumstances were combined with changes in parameters of the state of the systemic circulation and the microcirculation [2, 5]. We consider that the possible essential role of fibrinolysis factors in the regulation of hemostasis and of the rheologic properties of the blood in the pathogenesis of the ischemic and reperfusion syndromes of TCI must be taken into account.

The aim of this investigation was to study the dynamics of parameters characterizing the mechanisms of changes in fibrinolytic activity of the blood during coronary occlusion and in the initial stage of subsequent reperfusion of the myocardium.

EXPERIMENTAL METHOD

Experiments were carried out on 76 noninbred male albino rats weighing 200 ± 10 g. The animals were kept on an ordinary diet under animal house conditions. TCI was reproduced by the method described previously [3, 5]. All manipulations were done under urethane anesthesia (1200 mg/kg) under conditions of thoractomy and artificial ventilation of the lungs with atmospheric air. The duration of the period of MI was 10 or 40 min. The parameters of hemostasis were investigated at the 10th and 40th minutes of the subsequent reperfusion period (RP). The state of the fibrinolytic system of the blood was assessed by measuring changes in the activity of plasmin, plasminogen, plasminogen activator, and fibrinolysis inhibitors (antiplasmins, inhibitors of plasminogen activation) by the method in [7] in the modification [1], by determining the area of the zone of lysis under the influence of blood plasmin on standard fibrin disks. The outlines of the zone of lysis were transferred to washed, transparent x-ray films. The area of film corresponding exactly to the area of the zone of lysis of fibrin was cut out and weighed on torsion scales. Activity of the components of the fibrinolytic system of the blood was expressed (in accordance with the technique in [1]) in milligrams of x-ray film. The results were subjected to statistical analysis by parametric methods.

Significant changes in the state of the fibrinolysis system were observed not only during MI, but also during the subsequent RP.

During MI plasmin activity fell as early as by the 10th minute, and thereafter until the 40th minute it remained low (Fig. 1). One of the leading mechanisms of this phenomenon during coronary occlusion is a fall in the blood level of plasminogen and in the activity of its promoters, which was particularly marked at the 40th minute of local MI (Figs. 1b and 2b). Activity of fibrinolysis inhibitors, as follows from Fig. 2b, did not play any significant role in the development of this phenomenon.

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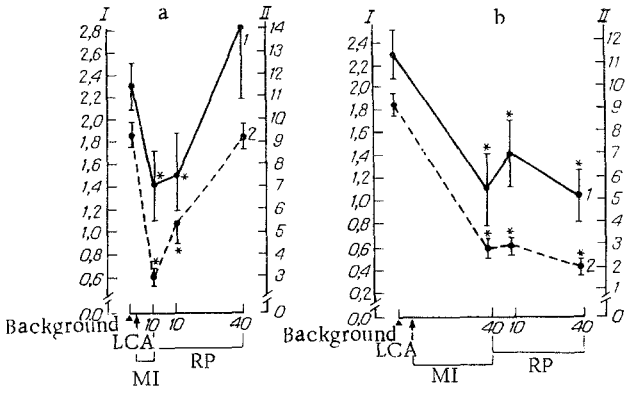

Fig. 1

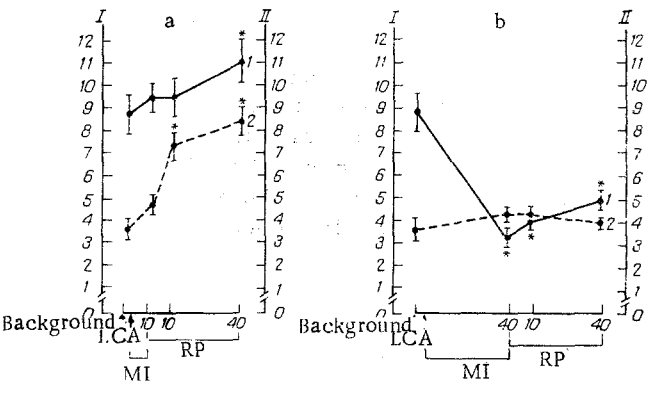

Fig. 2

Fig. 1. Plasmin and plasminogen activity of rat blood plasma during local MI of varied duration and subsequent RP (M ± mt). Abscissa, duration of periods of MI and of postischemic RP, min; ordinate: I) plasmin activity; II) plasminogen activity, mg of x-ray film. 1) Plasmin; 2) plasminogen. a) MI 10 min ± RP 40 min; b) MI 40 min + RP 40 min; LCA) ligation of coronary artery. *) Significant difference compared with background ($p < 0.05$).

Fig. 2. Activity of plasminogen activator and of fibrinolysis inhibitors of rat blood plasma during local MI of varied duration and subsequent RP (M ± mt). Abscissa, duration of periods of MI and of postischemic RP, min; ordinate: I) activity of plasminogen activator; II) activity of inhibitors, mg of x-ray film. 1) Plasminogen activator; 2) fibrinolysis inhibitors. Remainder of legend as to Fig. 1.

RP of the myocardium for 40 min after transient local ischemia was accompanied by elevation of plasmin activity to its background value (Fig. 1a). This was evidently to some extent the result of maintenance of a raised blood plasminogen activator level (Fig. 2a). Conversely RP of the previously ischemic myocardium, after a longer (40 min) period of coronary occlusion, was characterized by preservation of a depressed plasmin level. Under these circumstances low activity of fibrinolysis promoters, when activity of plasminogen inhibitors was close to the background range (Fig. 2b), indicates an essential role of the former in the development of this complication.

The results are in agreement with our previous observations [4] on staggered changes in the degree and rate of lysis of the fibrin-platelet structure (FPS) of the blood clot. These parameters were lowered in the period of coronary occlusion of TCI and were significantly changed during subsequent RP, depending on the duration of MI: after 10 min they were increased, but after 40 min they were reduced (especially the degree of lysis of the blood clot).

The results of this investigation suggest a leading role of changes in the plasminogen level and in the activity of its promoters in disturbances of activity of fibrinolysis reactions in both the ischemic and the reperfusion periods of TCI. Only during short-term ischemia and subsequent RP of the myocardium was the rise in activity of plasminogen promoters restrained by parallel activation of fibrinolysis inhibitors. It can also be tentatively suggested that one factor in depression of the process of lysis of fibrin during long-term (40 min) coronary occlusion, and also during subsequent RP of the myocardium is the utilization of plasminogen and plasmin in fibrinolysis reactions (the phenomenon of consumption of fibrinolysis factors).

The investigation thus had the following results:

1) local MI, whether of short (10 min) or long (40 min) duration, depresses fibrinolysis reactions, and this is accompanied, as we showed previously [2, 4, 5], by activation of the cellular and humoral components of hemostasis;

2) RP of the myocardium after short-term local myocardial ischemia is accompanied by normalization of the majority of parameters of the fibrinolytic system of the blood as early as by the 40th minute;

3) RP of the myocardium after long-term coronary occlusion is characterized by preservation of the low activity of factors of the blood fibrinolytic system, accompanied by hypercoagulation of the blood and by high contact activity of the platelets [4, 5]. In turn, these changes can potentiate the development of the no-reflow phenomenon — slow and incomplete restoration of the circulation in blood vessels of the microcirculatory system of the myocardium on resumption of the blood flow in the main branches of the coronary arteries after prolonged coronary occlusion [2, 5, 6, 8], and also lead to disturbances of the systemic hemodynamics under TCI conditions.

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