ARTERIOVENOUS DIFFERENCE IN ANTITHROMBIN III ACTIVITY AND ANTI-AGGREGATION PROPERTIES OF THE BLOOD VESSEL WALL

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KEY WORDS: thromboresistance; thrombogenesis; antithrombin III activity; anti-aggregation properties of the blood vessel wall.

The existence of a considerable difference between the formation, structure, and size of thrombi in arterial and venous systems is generally accepted [12]. However, the mechanism of this difference and factors directly or indirectly leading to its appearance, although they have attracted the attention of many investigators, remain unexplained.

The writers have postulated differences in the thromboresistance of arteries and veins, which correlates significantly with the activity of the principal endogenous universal anticoagulant antithrombin III and with the antiaggregation properties of the vessel walls. The aim of the present investigation was to find evidence in support of this hypothesis.

EXPERIMENTAL METHOD

Antithrombin III activity in arterial and venous blood and antiaggregation activity of the abdominal aorta and inferior vena cava were studied in 36 male Wistar rats weighing 150-180 g. Under pentobarbital anesthesia a midline incision was made in the anterior abdominal wall. Blood was taken from the aorta at its bifurcation in animals of one group, and from the inferior vena cava in rats of another group. The blood was mixed with 3.14% sodium citrate solution (9:1) and platelet-enriched and platelet-deprived plasma was obtained by differential centrifugation. Thrombin time was determined [6] in the platelet-enriched plasma and antithrombin III activity [7] in the platelet-deprived. In animals of the 3rd group, the abdominal part of the aorta and the inferior vena cava were removed. The vessels were rinsed in Tris-HCl buffer (0.05 M, pH 7.5) at 0°C and kept in a vessel with melting ice until the investigation began. The antiaggregation activity of the vessel was investigated as the degree of inhibition of ADP-induced platelet aggregation [1] on a "Crono Log" aggregometer. The results were subjected to statistical analysis.

EXPERIMENTAL RESULTS

As Table 1 shows, the thrombin time of platelet-enriched plasma obtained from arterial blood was on average 24% higher than from venous blood ($P < 0.05$).

TABLE 1. Antithrombin III Activity of Arterial and Venous Blood and Antiaggregating Activity of Blood Vessels

Parameter	Aorta	Vena cava
Thrombin time, sec	24,7±0,86	18,8±0,65*
Antithrombin III activity, %	212,0±17	156,0±0,23*
Degree of inhibition of ADP-induced platelet aggregation, %	60±16	10±1,6*

Legend. *$P < 0.05$.

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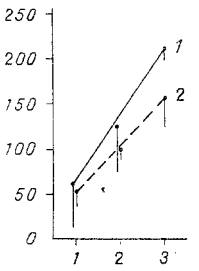

Fig. 1. Determination of antithrombin III activity during incubation of defibrinated arterial (1) or venous (2) blood plasma with thrombin solution (initial activity of thrombin 15 sec). Abscissa, incubation time (in min); ordinate, thrombin time (in sec).

Antithrombin III activity in arterial blood was 26% higher on average than in venous blood. According to the results of determination of antithrombin III activity, on incubation of thrombin solution (initial activity 15 sec) with test defibrinated plasma, the thrombin activity fell during incubation, and the greatest decrease was observed after 3 min (Fig. 1). Incubation of defibrinated arterial blood plasma with thrombin caused a greater decline in antithrombin III activity, indicating higher antithrombin III activity of arterial blood and the existence of an arteriovenous difference in this activity in healthy animals. The aorta had higher antiaggregating activity (Table 1). Incubation of the wall of the aorta with platelets from healthy animals caused inhibition of ADP-induced platelet aggregation on average by 60 ± 16%, and incubation of the wall of the vein inhibited it by 10 ± 2.6% ($P < 0.05$), i.e., the antiaggregating activity of the aorta on average was 83% higher.

It can be concluded that the more marked thromboresistance of the aortic wall and the arteriovenous difference are due to the high anticoagulant activity of arterial blood and the high antiaggregating activity of the arterial endothelium. Antithrombin III, the most powerful direct-action endogenous anticoagulant, blocks the action of the activated factors of the hemostasis system (thrombin, Xa, IXa, XIa, and VIIa) and it is the principal cofactor of heparin (wihtout it heparin is inactive) [2, 10]. The antiaggregation properties of the vessel wall are due mainly to continuous synthesis of prostacycline, the most powerful endogenous inhibitor of platelet aggregation [9].

The arteriovenous difference in antithrombin III activity may be due to two interconnected factors. First, we know that endothelial cells synthesize antithrombin III [8]. The total area of the endothelium lining the vessels of the lungs is much greater than that of other organs. If the vascular endothelium is directly involved in antithrombin III synthesis and if its activity in arterial blood is higher than in venous, this suggests that the lungs are among the central organs which regulate hemostatic homeostasis, and in that way they participate in maintaining the high thromboresistance of the arterial walls. Second, the decrease in antithrombin III activity as blood passes through the vessels of the systemic microcirculation may be due to consumption of this factor in the microcirculation itself. According to data in the literature [3, 4], continuous physiological microclotting takes place in the vessels of the microcirculation [3, 4]. If this is so, inactivation of the activated factors of the hemostasis system (XIa, etc.) is a protective physiological reaction, which may lead to consumption of antithrombin III and to a decrease in its activity in the venous blood. It has been shown [11] that the antithrombin–heparin complex may become fixed on the vascular endothelium during activation of the hemostasis system, and this plays an important role in maintenance of the thromboresistance of the vessel wall. Dependence of prostacycline synthesis on antithrombin III activity, i.e., a connection between the vessel wall and coagulation hemostasis, cannot be ruled out: Prostacycline increases antithrombin III activity [5]. High antithrombin III activity in arterial blood and higher antiaggregating activity of arterial vessels were thus found, and it may be these features which determine the higher thromboresistance of the arterial than of the venous wall.

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REGULATORY ROLE OF ADRENERGIC STRUCTURES IN INTESTINAL RELEASE OF BLOOD CLOTTING COMPOUNDS INTO THE BLOOD STREAM

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It was shown previously that the intestine has a significant effect on the hemostatic potential of regional blood, into which is secreted a number of blood clotting factors, anticoagulants, and fibrinolytic compounds [3, 8]. Acetylcholine receptors of the intestine are responsible for the intensity of antithrombin III release into the bloodstream [4].

The aim of this investigation was to study the regulatory role of adrenergic structures in the intestinal release of clotting and anticlotting factors into the bloodstream of the organ.

EXPERIMENTAL METHOD

Experiments were carried out on 36 cats of both sexes weighing from 2 to 3.5 kg. Under pentobarbital anesthesia (40-50 mg/kg, intraperitoneally) laparotomy was performed, the whole of the small intestine was isolated humorally, and the cranial mesenteric artery and vein were cannulated. Oxygenated Ringer–Locke solution for warm-blooded animals, warmed to 38°C, was pumped under a pressure of 216-16.7 kPa and at the rate of 20 ml/min through the artery. Samples of perfusate were taken every 10 min for 40 min (four samples). In the experimental series adrenalin hydrochloride (from Moscow Endocrine Factory, 37-212 nM), tropaphen* (from Kaunas "Sanitas" Factory; 3-6 mg/liter) or propranolol (Obsidan, from VEB Arzneimittelwerk, Dresden, East Germany) in the same dose was added to the perfusion solution. A solution containing the preparation was connected 18-19 min after the beginning of perfusion. Thus the second, third, and fourth samples were obtained 1-2, 10, and 20 min after injection of the drug into the vessels. There were four series of experiments: control, with adrenalin, with tropaphen, and with propranolol. The effect of the perfusate was studied on the following coagulation parameters: recalcification time of platelet-free plasma [6], prothrombin time of accelerin-free plasma [12], antiheparin activity [1], antithromboplastic activity [2],

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

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