TABLE 1. Characteristics of β-Adrenoreceptors of Chinese Hamster Fibroblasts

Experimental conditions	Number of β-receptors, fmoles/mg protein	K_d of receptor–dihydroalprenolol complex, nM
Control	351±46	13,4±2,2
Desensitization	343±31	12,6±2,4

ity of the agonist (in this case isoproterenol) to stimulate the cAMP system and to exert its radioprotective effect is lost. However, the presence of β-receptors capable of interacting with isoproterenol by itself is insufficient to enable realization of its antiradiation potential: Integrity of the adenylate cyclase system is an important condition.

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ANTITHROMBIN III ACTIVITY IN SLOWLY DEVELOPING HYPERCOAGULATION IN ANIMALS

V. E. Pastorova, G. G. Bazaz'yan, and L. A. Lyapina

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It has been shown that during "snowballing" thrombinogenesis rapid inactivation of thrombin by antithrombin III (ATIII) takes place in the blood stream of animals. The blood ATIII activity falls considerably under these circumstances [9, 16]. For instance, on intravenous injection of tissue thromboplastin into animals, a protective response of the anticlotting system is effected by the large quantity of thrombin that is formed rapidly in the blood, and is aimed at neutralizing the enzyme and preventing thrombin. This response is characterized by lengthening of the recalcification time and thrombin clotting time of blood plasma, a decrease in the fibrinogen concentration, an increase in the heparin concentration, and activation of enzymic and nonenzymic fibrinolysis [4]. Activity of ATIII falls under these circumstances from the first minutes after injection of thromboplastin, and this points to the direct and rapid participation of this inhibitor in the response of the anticlotting system [9]. In cardiovascular pathology, myocardial infarction, atherosclerosis, diabetes, and ischemic heart disease some workers have observed a decrease in ATIII activity [15], whereas others, in the same conditions, either found no change in the level of this inhibitor [11, 12]

Laboratory of Physiology and Biochemistry of Blood Clotting, M. V. Lomonosov Moscow University.

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TABLE 1. ATIII Activity during Slowly Developing Hypercoagulation in Old Rats

Group of animals	Number of animals	TFA, mm²	NEF, mm²	ATIII, %	Plasma heparin tolerance, sec	Thromboelastogram index, sec	
						R	K
Young (4-5 months)	28	50,5±5,3	20,0±3,1	121±4,0	877±120	99,1±6,0	53,0±2,7
Old (12-18 months)	24	40,4±3,5	15,9±1,1	18,3±15,2	323±28	83,3±5,2	39,0±2,0
P		>0,5	>0,5	<0,01	<0,01	<0,05	<0,05

or discovered an increase in its activity [7, 8]. It can be postulated that changes taking place in blood ATIII activity depend on the degree of disturbances in the hemostasis system. For instance, elevation of the ATIII level perhaps reflects a compensatory response of this inhibitor, during slow and protracted development of hypercoagulation in the initial stage of depression of function of the anticlotting system, against microquantities of thrombin appearing and circulating in the blood stream.

In the investigation described below ATIII activity was studied during the relatively slow (not "snowballing") development of hypercoagulation in intact old animals and in animals kept on an atherogenic diet.

EXPERIMENTAL METHOD

Old intact male rats aged 12-18 months and weighing 400-450 g were used in the experiments of series I. Rats aged 4-5 months, weighing 200-250 g, served as the control. The animals received the ordinary laboratory diet. In the experiments of series II rats kept on an atherogenic diet and rats receiving Wilgram's diet [2] for 3.5-6.5 months were used. Blood for analysis was taken from the jugular vein of the animals. Fibrinolytic activity of the plasma was determined by Bidwell's method in the modification in [1]. Total fibrinolytic activity (TFA) and nonenzymic fibrinolysis (NEF) were determined on fibrin disks, unstabilized with factor $XIII_a$, by the method in [6]. Plasma heparin tolerance was studied by the method in [13] and ATIII was determined by the method in [14]. Activity of the blood clotting system was judged by the values of parameters R and K of the thromboelastogram, obtained on the "Tromb-2" thromboelastograph. In this test, 0.1 ml of 1.29% $CaCl_2$ solution was added to 0.26 ml of citrated plasma.

EXPERIMENTAL RESULTS

It was shown previously that old rats develop certain signs of depression of function of the anticlotting system and a state of hypercoagulation: a raised blood fibrinogen concentration, lowered fibrinolytic enzyme activity and heparin concentration, and a decrease in the values of R and K of the thromboelastogram [3]. However, the TFA and NEF values did not fall significantly but showed only a tendency to decrease [5].

Table 1 shows that the old animals developed a state of hypercoagulation, as shown by the decrease in the values of R and K of the thromboelastogram and a fall in the heparin level. At the same time, there was a marked increase in ATIII activity (on average by 60%) compared with this parameter in young animals. In a few animals ATIII activity was increased by 200-250%. The TFA and NEF levels were somewhat lower than the control in this case, but the decrease was not significant.

The definite increase in ATIII activity during slowly developing hypercoagulation thus points to a protective and compensatory role of this inhibitor against the increased concentration of circulating thrombin. It will also be noted that there was no depression of NEF function in the animals at this stage of hypercoagulation, indicating prolonged preservation of the protective function of this important member of the anticlotting system.

In the experiments of series II signs of depression of function of the anticlotting system and of hypercoagulation (a decrease in enzymic fibrinolysis, an increase in the fibrinogen concentration and the plasma heparin tolerance, a decrease in the values of R and K of the thromboelastogram) were observed to appear in animals kept on an atherogenic diet in the course of 3.5-4 months. The ATIII level was significantly higher than in the control, but the increase was less than in old animals. TFA and NEF were at the normal level under these circumstances (Table 2). Only in animals kept on an atherogenic diet for 6 months or more, besides further development of depression of function of the anticlotting system and an in-

TABLE 2. Parameters of Anticlotting System in Rats Kept on Atherogenic Diet for 3.5 and 6.5 Months

Group of animals	Number of animals	TFA, mm²	NEF, mm²	Fibrinolytic activity, %	ATIII, (%)	Plasma heparin tolerance, sec	Thromboelastogram index, sec	
							R	K
Control (laboratory diet)	12	100±0	100±0	16±4,0	120±6,3	741±61	160±9,6	120±6,6
Experiment (atherogenic diet)								
3½ months	10	91±5,2	96±6,1	6±2,8	137±2,0	290±25	80±5,0	60±6,3
P		>0,5	>0,5	<0,05	<0,05	<0,01	<0,01	<0,01
6½ months	10	68,3±4,8	59,0±14	4,2±1,9	99,7±2,9	200±25	60±7,0	35±8,2
P		<0,05	<0,05	<0,05	<0,05	<0,01	<0,01	<0,01

crease in hypercoagulation, a gradual decrease was observed in ATIII activity, initially to the control level, but later as the rats continued on their atherogenic diet it fell below the control level. NEF and TFA also were lower in animals kept for a long time on the atherogenic diet (6.5 months) than in the control.

Thus in old animals and in animals in the initial period of development of depression of function of the anticlotting system as a result of being kept for 3.5 months on an atherogenic diet, increased ATIII activity in the blood can be regarded as a compensatory protective reaction of this inhibitor against microquantities of thrombin formed in the blood stream. This response arises during a slowly developing, but not during a "snowballing" increase in thrombin production in the blood stream. With intensification of hypercoagulation and with a further rise in the blood thrombin concentration, ATIII activity begins to fall gradually, and this is accompanied by the development of lasting depression of function of the anticlotting system (Table 2). When the state of hypercoagulation is due to a "snowballing" rise in the circulating thrombin level (for example, after intravenous injection of tissue thromboplastin into animals or if large quantities of thromboplastic substances are released from the tissues during surgical operations), ATIII activity falls rapidly and considerably because of its participation in emergency inactivation of the large quantities of thrombin that have been formed [8].

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