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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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TABLE 1. Effect of Adrenalin, Tropaphen, and Propranolol on Release of Tissue Blood Clotting Compounds into Intestinal Perfusate ($\bar{x} \pm m$)

Parameter, sec	Exptl. conditions	Control	Test sample of perfusate			
			1st	2nd	3rd	4th
Recalcification time of platelet-free plasma	Control	226,9±9,2	171,6±5,7	188,4±7,5	199,4±8,4	212,1±9
	Adrenalin	218,3±2,4	167,5±3,2	141,9±9,5***	181,0±4,9	195,8±3,7
	Tropaphen	233,0±3	170,0±11	200,0±8,9	214,8±4,2	227,4±4,4
	Propranolol	228,3±3	171,1±1,6	184,6±3,1	198,8±4	205,4±3,8
Prothrombin time of plasma deficient in factor V	Control	89,2±4,2	52,3±2,4	63,4±3,5	73,9±4,2	80,3±3,2
	Adrenalin	88,9±1,9	50,7±2,1	49,4±2,6**	66,3±2,8	77,9±1,9
	Tropaphen	88,0±2,4	51,5±1,4	69,0±2,4	77,5±3,6	80,4±3,2
	Propranolol	87,1±1,4	49,4±2,5	62,1±4,1	72,4±2,8	79,5±2,5
Antiheparin activity	Control	145,1±3,1	122,1±2,2	127,8±2,5	133,5±2,6	137,6±2,4
	Adrenalin	142,2±3,5	122,5±2,6	113,1±2,2****	124,1±2,5*	135,6±3,3
	Tropaphen	144,5±1	120,1±3	129,9±1,8	135,0±2,1	139,0±1,7
	Propranolol	146,4±1,4	121,3±0,8	124,1±0,9	131,0±1	136,1±0,8
Antithromboplastic activity	Control	6,8±0,2	9,5±0,4	9,0±0,4	8,4±0,3	8,1±0,3
	Adrenalin	6,7±0,1	9,6±0,2	8,0±0,1*	8,2±0,1	8,1±0,1
	Tropaphen	6,8±0,4	9,2±0,2	10,7±0,3**	10,6±0,3****	10,2±0,3***
	Propranolol	6,9±0,3	9,4±0,2	6,3±0,2****	6,7±0,3***	6,8±0,3**
Plasma thrombin time	Control	30,0±0,8	27,6±1,1	28,1±1	28,4±1	28,6±0,9
	Adrenalin	29,8±0,4	27,4±0,3	26,7±0,4	27,5±0,4	28,2±0,3
	Tropaphen	29,9±0,2	27,5±0,2	28,5±0,1	28,6±0,1	29,2±0,2
	Propranolol	29,9±0,2	27,5±0,1	27,8±0,1	28,4±0,2	28,6±0,2
Antithrombin III activity	Control	45,1±0,4	42,2±0,6	42,9±0,6	43,6±0,5	44,0±0,5
	Adrenalin	45,0±0,4	42,1±0,1	41,5±0,4	42,6±0,2	43,6±0,1
	Tropaphen	44,9±0,7	42,4±0,9	42,8±0,8	43,5±0,9	44,3±0,7
	Propranolol	45,2±0,5	42,1±0,6	42,9±0,7	43,6±0,7	43,9±0,6

Legend. *P < 0.02, **P < 0.01, ***P < 0.002, ****P < 0.001.

and thrombin time of plasma [5], and antithrombin III activity [10]. Blood clotting activity of the perfusate was determined by the method described previously [3].

EXPERIMENTAL RESULTS

The study of the intestine perfusate in the control series showed that thromboplastin, an analog of plasma factor V, antiheparin compounds, and antithromboplastins are secreted into the bloodstream from the vessels and tissues of the intestine (Table 1). Evidence of this was given by the ability of the perfusate to shorten the recalcification time of platelet-free plasma, the prothrombin time of plasma deficient in Ac-globulin, and the thrombin time of heparinized plasma and to inhibit clot formation on determination of its antithromboplastic activity. The total antithrombin activity of the plasma and its antithrombin III activity were reduced by the action of a solution which had passed through the intestinal vessels. This took place as a result of partial neutralization of the heparin and, perhaps, of the antithrombin III of the blood plasma by the antiheparin compounds of the perfusate.

Only 1-2 min after its addition to the perfusion solution adrenalin considerably increased the release of intestinal thromboplastin, accelerin-like factor, and antiheparin compounds into the bloodstream. The second sample of perfusate in the experimental series reduced the plasma recalcification time by 24.7%, the prothrombin complex time of plasma deficient in Ac-globulin by 22.1%, and the thrombin time of heparinized plasma by 11.5% more strongly than in the control series. Adrenalin significantly inhibited the outflow of intestinal antithromboplastins into the perfusate but had no effect on the antithrombin properties of the intestine. The action of adrenalin was exhibited only during the first minutes of perfusion, due to the instability of the compound in weakly alkaline Ringer—Locke solution and its rapid breakdown.

α-Adrenoreceptor blockade by tropaphen caused moderate weakening of the coagulating properties of the intestinal perfusate, due to a marked increase in the release of antithromboplastins from the vessels and tissues of the organ (Table 1). Compared with the control series, their activity in the second, third, and fourth samples of perfusate increased by 18.9, 26.2, and 25.9% respectively. Tropaphen had virtually no effect on the intensity of release of other compounds into the intestinal bloodstream. During β-adrenoreceptor blockade by propranolol the experimental samples of perfusate increased their procoagulant activity a little. The recalcification time of platelet-free plasma under the influence of these samples was shortened, although not significantly, compared with that in

the control. This was due to a decrease in the antithromboplastin concentration in the intestinal perfusate. Their activity fell by 30, 20.2, and 16% compared with the control. The concentration of other compounds in the intestinal perfusate was unchanged under the influence of propranolol.

It can be concluded that adrenalin is a powerful stimulator of release of certain blood clotting compounds and, of thromboplastin plasma factor V analog, and antiheparin substances, from the vessels and tissues of the intestine. The inhibitory effect of adrenalin on release of antithromboplastins into the bloodstream is evidently connected with excitation of α-adrenoreceptors. Release of antithromboplastins in the intestine is controlled with the aid of structures similar in their properties to α- and β-adrenoreceptors. The effects of adrenalin, however, in the intestine are realized not only through these, but probably also through other adrenergic structures which give little response to the antagonists which we used. This conclusion is confirmed by the results of investigations which showed differences in the properties of receptors responding to adrenalin [7, 9, 11].

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