ELECTROGENIC MECHANISM OF SECRETION OF COAGULATION FACTORS

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Changes in the permeability of the cell membranes of the vessel wall and of the nerve accompanied by a change in their electrical resistance lead to the liberation of coagulation factors into the medium. These factors may be membrane phospholipids which, when liberated into the cytoplasm, must modify its colloid state.

KEY WORDS: electrical impedance of the vessel; coagulation factors; adrenalin; choline chloride.

The blood vessel wall and blood cells contain large amounts of substances that affect blood clotting [1, 2, 10]. In certain states of the body these compounds are released and this is reflected in the coagulation and fibrinolytic properties of the blood [7-9, 20]. Liberation of the blood clotting factors from the vessel wall is accompanied by electrical activity [4-6, 11], i.e., according to the modern theory of biopotential generation, by a change in the permeability of the membrane with respect to sodium, potassium, and chlorine ions [14, 15]. The most adequate parameter of permeability in this case is the electrical impedance.

The relationship between this physical parameter and the process of secretion of the blood clotting factors from the vessel wall was investigated.

EXPERIMENTAL METHOD

The release of blood clotting factors and the electrical impedance of the vessel in response to injections of adrenalin and choline chloride were investigated in 18 dogs (weight 6-18 kg). Adrenalin (0.1%) and choline chloride (20%) were injected intravenously in a dose of 0.1-0.15 ml/kg body weight. The humorally isolated segment of the common carotid artery was perfused with physiological saline at 37°C. The effect of the perfusion fluid collected at consecutive 1-min intervals on the coagulation indices of platelet-deprived dog plasma was studied. The electrical impedance was recorded by means of platinum electrodes applied to the intima and adventitia of the vessel. The electrodes were connected into one arm of a measuring bridge powered by an audiofrequency generator (2000 Hz, 0.5 V). The voltage of imbalance, proportional to the change in impedance, was recorded after amplification and detection by means of a type N-340 galvanometer.

EXPERIMENTAL RESULTS

The dynamics of the coagulation indices under the influence of the perfusion fluid are shown in Table 1.

Analysis of the results shows that adrenalin and choline chloride induce the liberation of thromboplastic factor, substances with antiheparin activity, and fibrinolytic agents from the vessel wall. The liberation of these compounds with coagulation activity took place most intensively 1-2 min after injection of the preparations, and liberation of the fibrinolytic agents 5-6 min after their injection. The appearance

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TABLE 1. Effect of Perfusion Fluid Passed through the Common Carotid Artery of a Dog on Coagulation Indices in Response to Injection of Choline Chloride and Adrenalin

Index	Before perfusion	Perfusion fluid: before injection of preparations			Perfusion fluid: after injection of preparations							Preparations
		1	2	3	4	5	6	7	8	9	10	
R	138	121	122	123	116	114	122	123	125	123	138	
$\pm m_1$		5,0	2,2	3,8	2,1	2,2	3,2	2,9	2,7	3,1	4,2	
P_1		0,02	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01	—	
$\pm m_2$		—	—	—	2,0	2,5	2,7	—	4,3	—	3,8	
P_2		—	—	—	—	—	—	—	—	—	—	
T	39	38	38	36	35	34	36	36	37	37	37	
$\pm m_1$		0,7	0,6	0,7	0,9	1,2	1,1	0,9	0,9	0,6	0,7	Adrenalin
P_1		—	—	0,01	0,01	0,01	0,05	0,02	0,1	0,02	0,05	(n = 10)
$\pm m_2$		—	—	—	3,8	3,9	4,0	3,7	4,2	4,4	3,9	
P_2		—	—	—	—	—	—	0,02	0,05	0,01	0,1	
F	83	73	76	76	79	74	72	63	65	60	68	
$\pm m_1$		4,2	3,7	3,2	4,1	3,7	3,6	3,8	3,7	4,5	4,1	
P_1		0,1	0,1	0,1	—	0,05	0,02	0,01	0,01	0,01	0,01	
$\pm m_2$		—	—	—	3,8	3,9	4,0	3,7	4,2	4,4	3,9	
P_2		—	—	—	—	—	—	0,02	0,05	0,01	0,1	
R	124	114	111	113	106	89	110	117	143	116	115	
$\pm m_1$		6,4	5,7	4,1	3,8	3,7	3,9	4,1	3,9	4,2	3,7	
P_1		0,3	0,1	0,05	0,01	0,01	0,01	0,2	0,01	0,1	0,05	
$\pm m_2$		—	—	—	2,9	3,1	3,7	3,2	4,3	3,1	2,9	
P_2		—	—	—	0,05	0,01	—	0,3	0,01	—	—	
T	39	37	38	40	37	34	38	38	39	37	40	
$\pm m_1$		0,8	0,7	0,6	0,8	0,9	0,7	0,5	0,8	0,7	0,6	Choline chloride
P_1		0,05	0,2	0,2	0,05	0,01	0,2	0,1	—	0,05	0,2	(n = 8)
$\pm m_2$		—	—	—	0,7	0,9	0,9	0,7	0,8	0,7	0,9	
P_2		—	—	—	0,02	0,01	0,05	0,05	0,2	0,01	—	
F	95	97	90	92	99	94	90	74	62	68	67	
$\pm m_1$		5,2	6,4	4,8	7,2	4,5	4,3	6,8	6,7	5,8	4,2	
P_1		—	—	—	—	—	0,3	0,05	0,01	0,01	0,01	
$\pm m_2$		—	—	—	5,2	4,9	6,1	5,7	6,3	5,1	4,0	
P_2		—	—	—	0,2	—	—	0,05	0,01	0,01	0,01	

Legend. R) Recalcification time (in sec); T) thrombin time (in sec); F) fibrinolysis (in min). Statistical analysis carried out by the method of comparing, in pairs, results obtained before and after perfusion (m_1, P_1), and also before (sample 3) and after injection of the preparations (m_2, P_2).

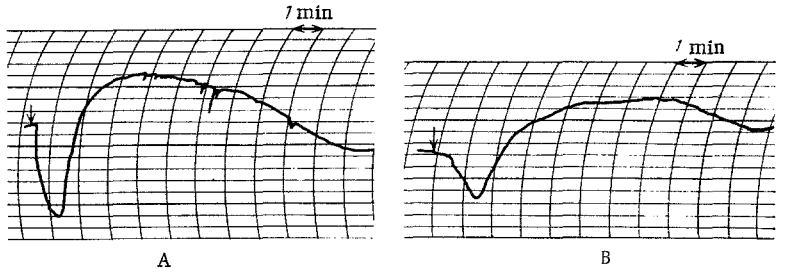

Fig. 1. Changes in electrical impedance of the common carotid artery after injection of adrenalin (A) and choline chloride (B).

of tissue clotting factors in the perfusion fluid was accompanied by biphasic changes in electrical impedance (Fig. 1). Immediately after the injection the impedance fell sharply, and this was followed by a second and longer phase of increased impedance. It can be concluded from a comparison of these findings with the dynamics of liberation of the tissue compounds that the decrease in impedance in most cases correlated with the release of coagulation compounds, whereas the increase in impedance was connected with the liberation of fibrinolytic agents and, in some cases, of anticoagulants.

TABLE 2. Effect of Fluid Bathing Nerve on Recalcification Time of Autogenous Plasma (n = 10)

Index	C_0	C_1	E_1	E_2
R	107	108	99	117
$\pm m$	—	—	2,8	3,2
P	—	—	<0,05	<0,05

Legend. C_0) control; C_1) fluid collected before excitation of nerve; E_1) during excitation; E_2) after disconnecting current. Criterion of significance (P) indicated for differences between values C_1-E_1 and E_1-E_2.

The fact that the changes in electrical impedance and in the liberation of tissue blood clotting factors were similar in direction in response to injection of both adrenalin and choline chloride is of considerable interest. The impression was obtained that the liberation of these substances is determined principally, not by the specificity of the physiological response to the action of the drugs, but by the dynamics of the electrical parameters of the tissue.

The liberation of substances with coagulation activity from nerve tissue during conduction of the impulse was investigated in special experiments on a nerve–muscle preparation of the frog limb. A segment of the sciatic nerve (between the knee joint and the stimulating electrodes) was irrigated with Riger–Locke solution at 20°C. The solution was collected before, during, and after electrical stimulation (6) pulses/min, 0.2 V) stimulation, and its effect on the recalcification time of autogeneous plasma was studied.

As Table 2 shows, stimulation of the nerve induced the liberation of substances shortening the recalcification time from it. It must be emphasized that the shortening of the recalcification time was directly proportional to the increase in the duration and frequency of stimulation.

The results suggest that the liberation of coagulation factors in response to a change in the functional state of the tissue is determined by the permeability of the cell membranes and by the associated process of generation of electrical activity.

The "skeleton" of the cell membrane consists chiefly of phospholipids (phosphatidylethanolamine, phosphatidylcholine, phosphatidylserine, etc.) [12, 13], which have a well-marked thromboplastic action. Presumably at the moment of action potential generation, the increased permeability of the cell membranes is accompanied by local destruction of the phospholipid layer. Since the cell membrane has two surfaces, the liberation of phospholipids must take place both into the cytoplasm and into the surrounding medium. The appearance of these compounds in the cell possibly modifies the colloidal properties of the cytoplasm, leading to gelatinization. This explains the phasic changes in the viscosity of the cytoplasm of various cells during their excitation [3, 16, 18, 19], as well as the coagulation theory of cell damage [17].

The liberation of substances promoting gelatinization of the cytoplasm evidently is a protective reaction of the cell. With an increase in the permeability of the cell membranes the diffusion of molecules along the concentration gradients must in fact largely abolish the boundaries between regions distinguished sharply in their composition. The increase in viscosity of the cytoplasm is a mechanism which in the first stage may prevent or at least considerably weaken this effect of injury or excitation of the cells.

The cell membranes must thus be regarded as among the most important factors determining the colloidal state of the cytoplasm and of the extracellular fluids.

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