ROLE OF SPECIFIC ADRENERGIC AND CHOLINERGIC RECEPTORS OF THE BLOOD VESSEL WALL IN THE REGULATION OF BLOOD CLOTTING DURING STIMULATION OF THE VAGUS NERVE

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Experiments on dogs showed that if the specific adrenergic receptors of the blood vessel wall (α- and β-receptors) were blocked by phentolamine or inderal it still continued to produce tissue blood clotting factors after stimulation of the vagus nerve. No response of this type was observed to stimulation of the nerve after the cholinergic receptors had been blocked by atropine. It is concluded that hyperfibrinolysis and hypercoagulation developing after vagus nerve stimulation are due to excitation of cholinergic structures.
KEY WORDS: adrenergic and cholinergic receptors; vagus nerve; blood clotting.

Previous investigations [6, 11-14] showed that stimulation of the vagus nerve (the intact nerve, its peripheral and central ends) leads to the development of hypercoagulation and hyperfibrinolysis. This effect is largely due to the liberation of tissue thromboplastin and fibrinolytic agents from the blood vessel wall. However, the vagus nerve is known to contain both parasympathetic and sympathetic nerve fibers. Clearly, therefore, the reaction observed may depend on stimulation not only of cholinergic, but also of adrenergic structures, the stimulation of which always leads to the liberation of blood clotting factors from the vessel walls [1, 4, 6-8, 13, 14].

With this in mind it was decided to carry out an investigation in which the effects of the sympathetic and parasympathetic receptors on the liberation of tissue blood clotting factors from the blood vessel could be blocked during stimulation of the vagus nerve.

EXPERIMENTAL METHOD

Twenty dogs of both sexes weighing 12-22 kg were used. Under hexobarbital anesthesia a segment of the common carotid artery (on the left side of the neck) was isolated humorally. The isolated segment of the vessel was irrigated with phentolamine (blocking α-adrenergic receptors), inderal (blocking β-adrenergic receptors), or atropine. The same compounds were injected intravenously in a dose of 1 mg/kg. By carrying out the experiments in this way the specific receptors could be blocked not only in the isolated segment, but also in other parts of the vascular system. Against this background the peripheral end of the divided vagus nerve, connected with the vascular bed, was stimulated for 30 sec by an electric current (8 Hz, 10 mA).

The perfusion fluid from the isolated segment of the vessel was collected at least three times before and seven times after stimulation of the nerve. Later the effect of the perfusion fluids was determined on the plasma recalcification time [17], the prothrombin consumption [2, 3], the thrombin time [19], and the fibrinolytic activity of the blood [18].

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TABLE 1. Effect of Perfusion Fluid Obtained from Isolated Segment of Common Carotid Artery on Some Indices of Blood Clotting in Dogs before and after Stimulation of Peripheral End of Vagus Nerve Combined with Injection of Phentolamine and Inderal

Drug used	Index studied	Statistical parameter	Control	Perfusion fluids									
				before nerve stimulation			after nerve stimulation						
				1	2	3	4	5	6	7	8	9	10
Phentolamine	Recalcification time (sec)	M	154,0	98,0	96,0	96,0	77,0	92,0	95,0	99,0	90,0	93,0	89,0
		P		0,05	0,1	0,05	0,01	0,05	0,05	0,05	0,05	0,02	0,01
		P_1		0			0,001	0,2	—	—	—	—	—
	Prothrombin consumption (sec)	M	51,0	66,0	72,0	72,0	80,0	78,0	77,0	77,0	73,0	74,0	74,0
		P		0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01
		P_1					0,01	0,01	0,05	0,1	—	—	—
	Thrombin time (sec)	M	47,0	38,0	39,0	38,0	38,0	38,0	38,0	37,0	37,0	37,0	37,0
		P		0,05	0,05	0,05	0,05	0,1	0,05	0,05	0,05	0,05	0,05
		P_1					—	—	—	—	—	—	—
	Fibrinolysis (min)	M	40,0	32,0	32,0	34,0	30,0	34,0	33,0	31,0	32,0	32,0	32,0
		P		0,2	0,2	0,2	0,1	0,2	0,2	0,05	0,2	0,2	0,05
		P_1					0,2	—	—	—	—	—	—
Inderal	Recalcification time (sec)	M	128,0	109,0	108,0	115,0	94,0	96,0	97,0	96,0	101,0	104,0	98,0
		P		0,001	0,01	0,001	0,01	0,01	0,01	0,01	0,01	0,01	0,01
		P_1					0,01	0,02	0,02	0,02	0,05	0,05	0,02
	Prothrombin consumption (sec)	M	26,0	32,0	31,0	31,0	35,0	34,0	32,0	33,0	31,0	32,0	31,0
		P		0,01	0,01	0,02	0,01	0,01	0,02	0,02	0,02	0,02	0,02
		P_1					0,02	0,02	0,2	—	—	—	—
	Thrombin time (sec)	M	41,0	40,0	39,0	40,0	40,0	40,0	40,0	40,0	39,0	40,0	39,0
		P		0,2	0,01	0,2	0,5	0,2	0,2	0,1	0,2	0,2	0,05
		P_1					—	—	—	—	—	—	—
	Fibrinolysis (min)	M	42,0	35,0	34,0	34,0	33,0	34,0	32,0	32,0	32,0	31,0	26,0
		P		0,01	0,01	0,01	0,01	0,02	0,1	0,05	0,05	0,05	0,01
		P_1					—	—	0,5	0,5	0,2	0,2	0,05

Legend: Here and in Table 2, significance of differences calculated between control and experiment (P) and also between last sample of perfusion fluid before stimulation and sample after stimulation of vagus nerve (P_1).

TABLE 2. Effect of Perfusion Fluid Obtained from Isolated Segment of the Common Carotid Artery on Some Blood Clotting Indices in Dogs before and after Stimulation of Peripheral End of Vagus Nerve and after Injection of Atropine

Index studied	Statistical parameter	Control	Perfusion fluids									
			before nerve stimulation			after nerve stimulation						
			1	2	3	4	5	6	7	8	9	10
Recalcification time (sec)	M	118,0	73,0	73,0	82,0	79,0	80,0	84,0	80,0	87,0	84,0	82,0
	P		0,05	0,05	0,05	0,05	0,05	0,05	0,05	—	—	0,05
	P_1					—	—	—	—	—	—	—
Prothrombin consumption (sec)	M	32,0	52,0	51,0	52,0	52,0	51,0	48,0	51,0	47,0	50,0	48,0
	P		0,02	0,02	0,02	0,02	0,02	0,05	0,02	0,02	0,02	0,02
	P_1						—	—	—	—	—	—
Thrombin time (sec)	M	43,0	39,0	40,0	40,0	40,0	41,0	40,0	40,0	40,0	40,0	40,0
	P		0,05	0,05	—	—	—	0,02	0,05	—	0,05	0,05
	P_1					—	—	—	—	—	—	—
Fibrinolysis (min)	M	72,0	55,0	58,0	58,0	62,0	62,0	55,0	59,0	57,0	60,0	55,0
	P		0,02	0,02	0,05	—	—	0,05	0,05	0,02	0,05	0,02
	P_1					—	—	—	—	—	—	—

EXPERIMENTAL RESULTS

Blocking the α-adrenergic receptors with phentolamine did not prevent liberation of the tissue blood clotting factors by the vessel wall into the general circulation in response to electrical stimulation of the vagus nerve (Table 1). This was shown by the fact that the recalcification time became shorter still after stimulation of the nerve (sample 4), whereas the prothrombin consumption (samples 4-6) increased. The fibrinolytic activity remained unchanged.

In the experiments in which inderal was given after stimulation of the nerve thromboplastin appeared in the perfusion fluid, for the recalcification time (samples 4-10) was reduced and the prothrombin consumption (samples 4-5) increased. Fibrinolytic agents were liberated only on a small scale and only toward the end of observation (sample 10).

Perfusion fluid obtained from the isolated segment of the vessel after atropinization possessed thromboplastic activity and contained activators of fibrinolysis (Table 2). This was shown by the shortening of the recalcification time, the increased prothrombin consumption, and the decrease in the time of fibrinolysis. After stimulation of the vagus nerve the activity of the perfusion fluid remained unchanged.

In response to a flow of impulses travelling entirely along the cholinergic fibers of the vagus nerve, the blood vessel wall thus liberates tissue blood clotting factors into the bloodstream. This is shown by the liberation of blood-clotting compounds from the vessel wall in response to vagus nerve stimulation after preliminary perfusion of the segments of the vessel with phentolamine and inderal, blocking specific α- and β-adrenergic receptors, respectively. Meanwhile this property of the vessel wall disappears if the vagus nerve is stimulated after injection of atropine.

The liberation of tissue thromboplastin and activators of fibrinolysis in response to excitation of the parasympathetic division of the autonomic nervous system causes the blood to clot more rapidly and stimulates fibrinolysis [5, 6, 11-14].

The hypercoagulation and hyperfibrinolysis developing during stimulation of the vagus nerve are thus caused by excitation of cholinergic structures.

LITERATURE CITED

1. V. V. Bochkarnikov, The Mechanism of Action of Nitroglycerin on the Coagulability of the Blood and Fibrinolysis, Candidate's Dissertation, Barnaul (1972).
2. M. A. Kotovshchikov and Z. D. Fedorova, Lab. Delo, No. 1, 18 (1961).
3. B. I. Kuznik, Lab. Delo, No. 1, 34 (1962).
4. B. I. Kuznik, in: The Blood Clotting System and Fibrinolysis [in Russian], Kiev (1969), p. 88.
5. B. I. Kuznik, V. V. Al'fonsov, L. G. Voronyanskaya, et al., in: Proceedings of a Conference on Blood Clotting Problems [in Russian], Baku (1966), p. 156.
6. B. I. Kuznik, V. V. Al'fonsov, V. F. Rusyaev, et al., in: Problems in Neuro-Humoral Regulation of Blood Clotting under Normal and Pathological Conditions [in Russian], Chita (1971), p. 73.

7. B. I. Kuznik and V. P. Mishchenko, Farmakol. i Toksikol., No. 4, 463 (1967).
8. B. I. Kuznik and V. P. Mishchenko, Byull. Éksperim. Biol. i Med., No. 9, 29 (1968).
9. B. I. Kuznik, V. P. Mishchenko, and V. F. Rusyaev, Dokl. Akad. Nauk SSSR, 182, No. 2, 480 (1968).
10. B. I. Kuznik, V. P. Mishchenko, and V. F. Rusyaev, Cor et Vasa, 11, 146 (1969).
11. V. P. Mishchenko, in: Theoretical and Clinical Problems of Blood Clotting [in Russian], Saratov (1968), p. 130.
12. V. P. Mishchenko, in: The Blood Clotting System and Fibrinolysis [in Russian], Kiev (1969), p. 111.
13. V. P. Mishchenko, The Blood Vessel Wall as an Efferent Regulator of the Blood Clotting Process and Fibrinolysis, Doctoral Dissertation, Novosibirsk (1962).
14. V. P. Mishchenko, in: Proceedings of a Zonal Scientific Conference on Atherosclerosis, Hypertension, and Coronary Insufficiency [in Russian], Vladivostok (1972), p. 16.
15. V. P. Mishchenko, B. I. Kuznik, and V. V. Bochkarnikov, Cor et Vasa (Prague), 14, 223 (1972).
16. V. P. Mishchenko and V. F. Rusyaev, in: Proceedings of the Fourth Scientific Conference of Physiologists, Biochemists, and Pharmacologists of the Western Siberian Union [in Russian], Krasnoyarsk (1969), p. 311.
17. H. D. Bergerhof and L. Roka, Z. Vitamin-Hormon-Fermentforsch., 6, 25 (1954).
18. H. Kowatzyk and K. Buluk, Acta Physiol. Pol., 5, 35 (1954).
19. E. Szirmai, Probl. Gematol., No. 6, 38 (1957).