METHODS

A Model of Myocarditis

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 134, No. 7, pp. 112-113, July, 2002
Original article submitted June 20, 2002

Myocarditis was induced by synergic interactions of serotonin- and cholinergic nerve fibers during potentiation of vagal inhibition of cardiac activity by stimulation of the stellate ganglion. Thus modeled myocarditis was associated with increased content of serotonin and decreased concentrations of acetylcholine and catecholamines in the myocardial tissue. Blockade of 5HT3(S3) receptors in autonomic ganglia and 5HT1,2(S1,2) receptors in the myocardium improved myocardial contractility and reduced the severity of myocarditis.

Key Words: *model; myocarditis; stellate ganglion; vagus nerve; serotonin*

Changed balance between the sympathetic and parasympathetic nervous systems often leads to the development of myocarditis and gastroduodenal ulcers [1-3]. Reliable methods for modeling this process are needed for studying the pathogenesis of myocarditis and possible ways of its prophylaxis.

Available models of myocarditis (myocarditis induced by hypoxia or anoxemia, sensitization with foreign proteins, organic or inorganic chemicals) are traumatic. When studying the mechanism of potentiation of vagal inhibition of the cardiac function in case of simultaneous stimulation of the sympathetic and vagus nerves (VN) we observed the development of myocarditis in acute experiments on rabbits.

The purpose of the study was to develop a method for reproducing the clinical picture of myocarditis.

MATERIALS AND METHODS

Myocarditis was modeled in 42 rabbits. The rabbits were subjected to right-sided vagotomy 1.5-3 weeks before the experiment. In the acute part of the experiment the nerves and vessels were prepared under Hexenal or Nembutal narcosis, blood pressure in the right carotid artery and myocardial impedance were measured, isolated and combined stimulation of the left VN and right stellate ganglion (SG) were carried out. In experiments with combined stimulation SG was stimulated 5-10 sec after the start of VN stimulation (after stabilization of bradycardia).

VN and SG were stimulated for 40-60 and 10-20 sec, respectively. The nerves were stimulated with rectangular pulses (10-20 Hz, pulse duration 1.5-3.0 msec, pulse amplitude 5-15 V for SG and 1-7 V for VN).

β-Adrenoceptors were blocked with obsidan (1-3 mg/kg), 5HT1,2(S1,2) receptors with chlorpromazine (0.1-1.0 mg/kg), promethazine (1-2 mg/kg), and LSD (0.01-0.03 mg/kg); 5HT3(S3) receptors were blocked with morphine (0.1-0.2 mg/kg) and promedol (1-2 mg/kg).

Experimental animals were divided into 2 groups: group 1 (n=30) included rabbits weighing ≤3 kg and group 2 (n=12) consisted of rabbits weighing more than 3 kg (group 2 rabbits were 6 months older, on average, than group 1 animals).

The results were processed statistically using Student's t test.

RESULTS

The first experimental series demonstrated that SG stimulation added to VN stimulation against the back-

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0007-4888/02/1341-098$27.00

TABLE 1. Content of Transmitters in Myocardium during Experimental Myocarditis (*M*±*m*)

Transmitter	Atrium, mg/kg		Ventricle, mg/kg	
	control	experiment	control	experiment
Acetylcholine	2.60±0.08	1.35±0.01	1.65±0.05	0.93±0.01
Norepinephrine	4.00±0.07	3.50±0.04	1.95±0.03	1.35±0.04
Serotonin	15.40±0.11	22.50±0.14	7.10±0.02	8.9±0.1

Note. All differences from the control are significant ($p<0.05$).

ground of β-adrenoceptor blockade potentiated vagal inhibition of the cardiac function in 70% rabbits (group 1). Heart rate decreased by 10-15% during stimulation of the sympathetic nerve. In group 2 this phenomenon was more pronounced (heart rate decreased by 20-22%) and was more often observed (in 89% animals).

Fifteen minutes after reproduction of this effect the surface of the myocardium lost typical structure and looked polished in 5 (42%) rabbits of group 2 and in 5 (16%) of group 1. Systolic blood pressure decreased from 135.0±5.2 to 78.4±3.0 mm Hg and diastolic pressure from 74.0±6.0 to 47.0±4.7 mm Hg. Electrocardiography revealed decreased voltage of *R* wave (by 12.0±0.1%), flattening of *T* wave by 5.00±0.22%, and lengthening of *QT* interval by 9.0±0.1%.

The concentrations of acetylcholine and norepinephrine sharply decreased and that of serotonin increased within the first few minutes of myocarditis development (Table 1). Increased concentration of serotonin in myocardial tissue was associated with activation of preganglionic serotoninergic fibers forming synapses with serotoninergic efferent neurons. Parallel decrease in the concentrations of catecholamines and acetylcholine with simultaneous increase in serotonin concentration led to the development of myocarditis.

In both groups serotonin in doses of 0.1-0.3 ml (10^{-5}-10^{-6} g/liter) increased the severity and incidence of potentiation of vagal inhibition of cardiac activity by stimulation of the sympathetic nerve, without producing intrinsic chrono- or inotropic effects. These data suggest that serotoninergic elements are involved in the synergic activity of the sympathetic and parasympathetic nervous systems. The presence of pronounced inhibitory phenomenon or its increase by exogenous serotonin led to the development of myocarditis.

Effects of various drugs on the course of myocarditis were also investigated.

Blockade of 5HT3(S3) receptors in autonomic ganglia with morphine and promedol improved myocardial contractility. Blockade of myocardial 5HT1,2 (S1,2) receptors also improved myocardial function and prevented myocarditis. In the absence of blockade of serotoninergic structures 40-42% animals died within the first hour of myocarditis development, while their blockade reduced the mortality rate to 16%.

A possible mechanism of myocarditis development under condition of simultaneous stimulation of the sympathetic and parasympathetic nervous system is the increase in serotonin content in comparison with catecholamines and acetylcholine contents in the myocardial tissue.

Hence, simultaneous stimulation of VN and SG induces myocarditis similar by its pathophysiological mechanisms to clinical forms of myocarditis due to involvement of serotonin in the regulation of cardiac function.

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