PHYSIOLOGY

Parasympathetic Nervous System Modulates Effects of Hyperpolarization-Activated Channel Blockade

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Bilateral vagotomy eliminating extracardiac parasympathetic influences on the heart modulates the changes in variational pulsogram during blockade of hyperpolarization-activated currents, but has no significant effect on stroke volume after the blockade.

Key Words: *heart; hyperpolarization currents; nervous control; rat; vagus*

According to current views cardiac function is regulated by subdivisions of the autonomic nervous system (ANS): sympathetic system activates, and parasympathetic system inhibits both the chronotropic and inotropic function of the heart. However, the effects of simultaneous stimulation of sympathetic and parasympathetic cardiac nerves are not arithmetically added, which prompted some authorities to revise the concept of nervous control of cardiac function and to advance the theory of "accentuated antagonism" between sympathetic and parasympathetic influences [8,9]. Recently, an important role in the regulation of cardiac function, specifically, in the generation of pacemaker currents in the heart was assigned to hyperpolarization-activated currents (Ih). [1,2,7,10]. The currents activated by hyperpolarization are non-selective inward cation currents. They depolarize the membranes of atypical cardiomyocytes in the sinoatrial node from -60 to -40 mV [6]. Blockade of hyperpolarization-activated (H) channels suppresses pacemaker activity of the sinoathrial node due to prolongation of spontaneous diastolic depolarization. Activation of H-channels is modulated by intracellular cAMP concentration [11]. At the same time, experiments on rabbits showed that activation of H-channels was not accompanied by protein phosphorylation [3]. Experiments on pigs and rabbits with blocked H-currents allowed to hypothesize that cardiac rhythm is regulated by ANS via modulation of H-channels [4]. We previously showed that Ih blockade modulates the effect of electrical stimulation of rat vagus nerves [1,2].

Here we studied the modulating effect of bilateral vagotomy on changes in cardiac indices produced by Ih blockade in rats.

MATERIALS AND METHODS

Experiments were carried out on 20-week-old random-bred albino rats (n=15).

The rats were anesthetized intraperitoneally with urethane (1000 mg/kg, 25% solution). Ih currents were blocked with 4-(N-ethyl-N-phenylamine)-1,2-dimethyl-6(methylamine)pyrimidine chloride (ZD-7288, Tocris). The blocker (0.07 mg/kg) was injected into the right femoral vein. The right and 30 min later the left vagus nerves (VN) were cut.

Electrocardiogram (ECG) and rheogram were visually controlled using an S1-83 oscillograph. The signals were recorded and processed on a computer. The original software processed 21 parameters of ECG and variational pulsogram and 7 parameters of volumetric and tetrapolar rheograms.

The results were processed statistically using Student's t and Wilcoxon tests.

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RESULTS

Injection of ZD7288 after successive bilateral vagotomy induced bradycardia. On minute 5 postinjection, the mean cardiointerval (X_M) increased and attained a maximum 15 min postinjection (Table 1). The increase in *R—R* interval was less pronounced than in intact rats (X_M=47%, Fig. 1). Blockade of Ih after vagotomy modulated the parameters of variational pulsogram. These changes were similar to those caused by blocker injection before vagotomy, but were less pronounced. For example, in experimental rats the variational range (DX) increased only 1.7-fold, while in intact rats it increased 11.2-fold (Table 1). The strain index (SI) decreased to a lesser extent than in experiments, when ZD7288 was injected before vagotomy (Table 1). Other parameters of variational pulsogram also decreased (Table 1).

In vagotomized rats ZD7288 increased X_M due to prolongation of *T—P* interval and *T* wave (Table 1). In intact rats the same dose of Ih blocker increased *T—P* interval by 38% and duration of *T* peak by 55%, while preliminary vagotomy weakened the latter effect by 24%. The duration of other ECG intervals and waves little changed (Table 1).

Injection of ZD7288 after successive vagotomy slightly increased stroke volume (by 16%), while in intact rats the corresponding value was 22%. Therefore, preliminary blockade of parasympathetic influences produced no significant effect on changes in the stroke volume caused by Ih blockade.

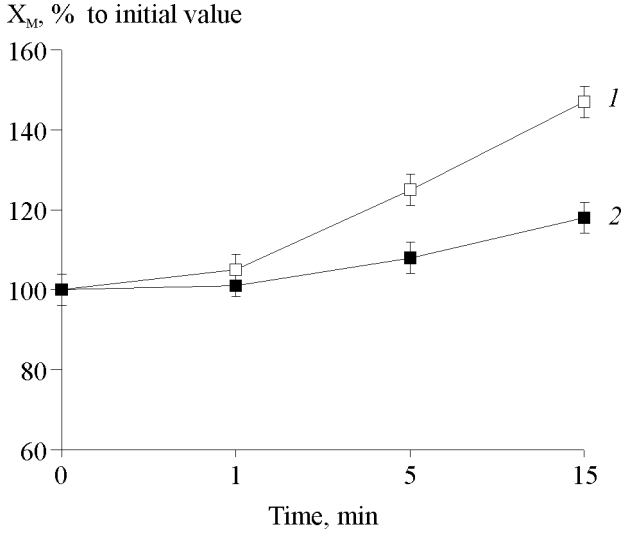

Fig. 1. Effect of ZD7288 (0.07 mg/kg) on mean cardiointerval (X_M)

Thus, Ih blockage after vagotomy induced bradycardia, modulated parameters of variational pulsogram, and increased stroke volume, although these changes were less pronounced than after ZD7288 injection before vagotomy (Fig. 1). These data suggest that ZD7288-induced bradycardia depends on activity of the parasympathetic system controlling the cardiac function.

TABLE 1. Effect of ZD7288 Injected in Intact Mature Rats before and after Vagotomy on Parameters of ECG and Variational Pulsogram (*M*±*m*)

Index	Vagotomy (*n*=7)		Intact (*n*=8)	
	initial	15 min	initial	15 min
R—R, msec	190.5±8.5	224.0±18.7	191.70±9.65	282.0±24.4**
ΔX, msec	4.3±0.4	7.2±2.0	4.8±0.9	53.8±34.9
δ	1.40±0.09	2.0±0.5	1.35±0.17	9.90±5.15
MA, %	35.3±1.9	29.0±4.7	39.7±4.7	18.3±4.9**
SI, arb. units	22,665±2890	14,908±5480	29,800±9306	3660±218
ABI, arb. units	8555±1041	6054±2099	10,500±2700	1630±874**
ARI, arb. units	1275±122	893±206	1418±402	263±105**
CC, arb. units	188.0±16.5	138.0±27.1	214.0±31.8	75±26*
T—P, msec	112.8±6.6	140.7±18.1	130.8±23.1	180.5±18.9
T, msec	79.0±7.3	98.1±6.8	49.2±3.0	76.0±7.4**
P, msec	23.0±1.1	26.3±2.4	21.0±2.8	27.3±2.8
P—Q, msec	62.7±2.1	66.7±1.9	56.2±4.1	66.5±4.97
P—Q/*R—R*	33.3±1.1	31.2±2.5	29.5±1.7	25±1
Q—T/*R—R*	8.00±0.01	7.7±0.2	15.70±0.21	13.3±1.6
SV, ml	0.231±0.033	0.269±0.040	0.285±0.044	0.347±0.053

Note. *p<0.001, **p<0.05 compared to initial values. Abbreviations: strain index (SI), mode amplitude (MA), autonomic balance index (ABI), autonomic rhythm index (ARI), standard deviation (δ), control conformity (CC), and variational range (ΔX).

The first data on pronounced bradycardia induced by Ih blockers suggested that the pool of H-channels could be one of the end elements of parasympathetic influences inhibiting cardiac activity. However, our findings on the effect of Ih blockade on the action of vagal electrical stimulation [1,2] contradict this hypothesis. Electrical stimulation of the right vagus augmented bradycardia against the background of significantly increased X_M after administration of Ih blocker. These data suggest that bradycardia during stimulation of preganglionic parasympathetic fibers in vagus and bradycardia during Ih blockade by ZD7288 are mediated by different mechanisms. Our previous data on the dose-dependent influence of Ih blockade on the effects of successive bilateral vagotomy also indicate on possibility of intermodulating influences of parasympathetic discharges and H-channels in the regulation of cardiac function [2].

Analysis of the data with Ih blockade should be performed with due account to possibility of blockade of these currents in intracardiac (specifically, in parasympathetic postganglionic) neurons. The possibility of this effect is indicated by recent data on intracardiac neurons isolated from rats of various age [5].

Thus, we may conclude, that parasympathetic subdivision of ANS modulates the performance of hyperpolarization-activated channels, and blockade of these channels affects parasympathetic control of the heart.

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