CHANGES IN STRUCTURE OF THE VAGUS EFFECT ON CARDIAC RHYTHM DURING PROCEDURES AIMED AT ALTERING THE ACTIVE ACETYLCHOLINE CONCENTRATION

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UDC 612.172.2+612.819.91

KEY WORDS: vagus nerve; burst stimulation; vagus chronotropic effect; tonic component; synchronizing component.

The purely inhibitory tonic action, manifested as slowing of the heart rate or even cardiac arrest, is not the only possible type of parasympathetic chronotropic influence reproduced by vagus stimulation. For instance, during stimulation of the vagus nerve by bursts of pulses synchronized with each cardiac contraction, the severity of the ensuing bradycardia depends essentially on the phase of the cardiac cycle in which the stimulus is applied to the nerve [3, 7, 8]. Within a certain range, bounded by the smallest and largest possible degree of slowing of the heart, any change in following frequency of the bursts is reproduced synchronously by the heart, so that controllable bradycardia is possible (Fig. 1). Thus the chronotropic effect of the vagus nerve includes not only the tonic component already known, but also the so-called synchronizing component, by means of which the cyclic activity of the heart can be controlled. Some neuropeptides have been shown to interact structurally and functionally with acetylcholine in the mechanism of regulatory influences on structures of the heart [10, 12]. It can accordingly be postulated that heterogeneity of the structure of the chronotropic vagus effect may be connected with involvement of noncholinergic mechanisms in the realization of the vagus effect on the cardiac rhythm. The aim of this investigation was to study the dynamics of the structure of the chronotropic vagus effect in the course of various procedures aimed at modifying the active concentration of acetylcholine.

EXPERIMENTAL METHOD

In 29 experiments on cats anesthetized with chloralose and pentobarbital (75 and 15 mg/kg respectively) the right vagus nerve was divided at the level of the thyroid cartilage and the animals were artificially ventilated. The peripheral end of the vagus nerve was placed on bipolar platinum electrodes and covered with a mixture of melted wax and mineral oil. The right vagus nerve was stimulated with bursts of square pulses from an ÉSU-2 electrical stimulator Bursts of 2, 3, 4, 6, and 9 pulses were used. Pulse duration and pulse generation frequency in the burst were 2 msec and 40 Hz respectively and the amplitude was 5-6 times the threshold value. By means of a unipolar probe, introduced through the femoral vein, electrograms of the right atrium were recorded by means of an ÉKPSChT-4 electrocardiograph with N338-4 automatic writer. The vagal chronotropic effect and its components – tonic and synchronizing – were calculated. The intensity of the latter was assessed from the width of the ranges of control of the cardiac rhythm. The magnitude of the tonic component was found as the difference between the initial heart rate (HR) and HR at the upper (relative to the initial cardiac rhythm) limit of the synchronization range. The total value of the vagal chronotropic effect was found as the sum of its components. As procedures aimed at modifying the acting acetylcholine concentrations we used: in the experiments of series I – injection of neostigmine, in experiments of series II – injection of the muscarinic cholinomimetic pilocarpine. Both drugs were injected intravenously by the jet method in doses of 0.003 and 0.03 mg/kg respectively. In the experiments of series III the dynamics

Department of Normal Physiology, Red Army Kuban Medical Institute, Krasnodar. Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 114, No. 12, pp. 570-573, December, 1992. Original article submitted February 25, 1992.

0007-4888/92/0012-1741$12.50

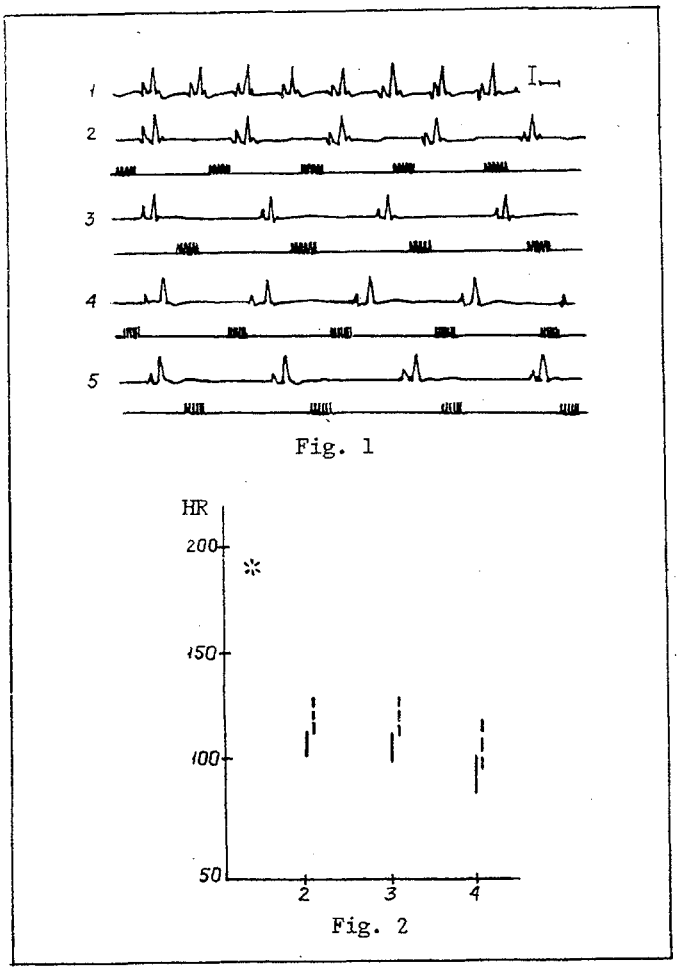

Fig. 1. Effect of neostigmine on synchronization of cardiac and vagus rhythms (stimulation of vagus nerve by 6 pulses): 1) initial cardiac rhythm, 2 and 3) upper and lower limits of synchronization range respectively, 4 and 5) the same, after injection of neostigmine. Calibration: 1 mV, 0.1 sec.

Fig. 2. Changes in ranges of controlled bradycardia during vagus stimulation for 5 min. Abscissa, number of pulses in burst; ordinate, heart rate. Continuous line represents ranges of controlled bradycardia per minute of vagus stimulation, broken line – after 5 min. *) HR before beginning of vagus stimulation.

of the structure of the chronotropic vagus effect was studied during long-term vagus nerve stimulation. The magnitude of the chronotropic vagus effect and of its components 1 min after the beginning of vagal stimulation and 5 min later was compared. The results were subjected to statistical analysis by the direct differences method [2].

EXPERIMENTAL RESULTS

In response to stimulation of the peripheral end of the vagus nerve ranges of synchronization of the cardiac and vagus rhythms were obtained within which the heart responded to each burst of pulses by a single contraction (Fig. 1). Injection of neostigmine (n = 11) evoked a regular increase in the chronotropic vagus effect, amounting to 13.3, 10.0, and 8.2% to stimulation by 3, 6, and 9 pulses respectively. However, the components of the chronotropic

TABLE 1. Effect of Neostigmine and Pilocarpine on Chronotropic Vagus Effect and Its Components

Procedure	Initial HR	Power of burst	Upper limit of synchronization range	Lower limit of synchronization range	Synchronizing component	Tonic component	Chronotropic vagus effect
		3	111,6±5,0	98,5±5,3	13,1±1,0	78,8±3,7	91,9±4,0
			100,5±5,1	90,3±5,5	10,2±1,6*	93,9±5,2*	104,1±5,1*
Neostigmine,	190,4±6,1						
0,003 mg/kg	194,4±8,6	6	99,4±4,7	81,6±4,1	17,8±1,6	91,0±4,7	108,8±4,5
			87,1±4,6	74,7±4,3	12,4±1,8*	107,3±6,4*	119,7±7,7*
		9	88,8±8,7	69,2±3,5	19,6±1,2	101,6±5,0	121,2±5,0
			76,3±4,4	63,3±4,0	13,0±1,4*	118,1±7,9*	131,7±7,9*
		3	117,5±5,1	103,6±4,7	13,9±2,3	73,8±6,4	87,7±8,1
			126,0±6,4	113,4±5,5	12,6±1,9	50,4±5,9*	63,0±6,3*
Pilocarpine,	191,3±7,5						
0,03 mg/kg	176,4±8,7*	6	102,2±3,6	84,6±3,2	17,6±1,9	89,1±6,8	106,7±8,5
			108,0±4,4	90,7±3,1	17,3±1,6	68,4±6,3*	85,7±7,5*
		9	90,9±3,6	72,4±2,6	18,5±1,4	100,4±8,2	118,9±8,2
			97,9±3,5	80,1±2,4	17,8±1,4	78,5±7,0*	96,3±7,9*

Legend. For each parameter top line gives initial value, bottom line after procedure. *$p < 0.05$.

vagus effect underwent unequal changes under these conditions. In particular, the cause of the increase in chronotropic vagus effect was an increase in its tonic component (Table 1), which amounted to 19.2, 17.9, and 16.2% for the same conditions of stimulation Meanwhile the synchronizing component did not increase but, on the contrary, it decreased significantly by 22.1, 30.3, and 33.7%.

Injection of pilocarpine (n = 9) caused the background HR to fall by 7.8%, Unlike in the experiments of series I, however, inhibition of the chronotropic vagus effect was observed in this case, its value amounting to 28.2, 19.7, and 19.0% respectively for stimulation by 3, 6, and 9 pulses. Since ligand-receptor interrelations of pilocarpine and acetylcholine, secreted during vagus nerve stimulation, are competitive in character, the effect may be the result of a decrease in the total number of free muscarinic acetylcholine receptors accessible for acetylcholine [4], or of their desensitization [1]. Inhibition of the chronotropic vagus effect was due to a decrease in the tonic component (Table 1), which amounted to 31.7, 23.2, and 21.8% respectively. Meanwhile there was no significant change in the synchronizing component.

It follows from the experiments of series III (n = 9) that the components of the chronotropic vagus effect undergo opposite changes in the course of long-term vagus stimulation. Stimulation of the vagus nerve for 5 min with bursts of 2, 3, and 4 pulses led to inhibition of the chronotropic vagus effect by 21.8, 15.7, and 9.2% respectively compared with values recorded after 1 min. This kind of effect may be associated with a decrease in the neuronal acetylcholine reserves [6], self-inhibition of presynaptic muscarinic acetylcholine receptors [11], or weakening of vagal hyperpolarization of cells of the sinoatrial node during long-term vagus nerve stimulation [5]. Inhibition of the vagus effect was due to a fall in the value of the tonic component by 24.1, 21.6, and 17.0%, whereas the synchronizing component was unchanged in response to stimulation by two pulses, but if three or four pulses were applied it actually increased by 23.4 and 32.9% respectively (Fig. 2).

The idea that the acting acetylcholine concentration is a factor determining the intensity of the parasympathetic chronotropic action must evidently be accepted as valid only in relation to purely inhibitory tonic vagus effects. The absence of any such dependence for cycle-synchronizing effects, responsible for the development of the phenomenon of cardiac rhythm control suggests a definite role of noncholinergic mechanisms in their genesis. The character of these mechanisms and the degree of their involvement in the creation of conditions for controlled bradycardia undoubtedly require further clarification. However, considering the widening of the range of controlled bradycardia observed during long-term vagus stimulation it can be concluded that a particular feature of the noncholinergic effect

in this case is the delayed character of the effect, which on the whole agrees with data in the literature on this problem [9].

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