SOMATOSTATIN AS MODULATOR OF VAGAL EFFECTS ON CARDIAC RHYTHM

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KEY WORDS: vagus nerve; burst stimulation; control of cardiac rhythm; somatostatin.

The role of peptidergic mechanisms in realization of vagal influences on the heart is now a well documented fact [4, 14]. It has been shown that some regulatory peptides may be localized together with acetylcholine in the parasympathetic neurons of the intramural ganglia of the heart [7, 14], and on this basis their combined secretion as a result of vagal stimulation has been postulated. This phenomenon is observed mainly during high-frequency periodic or burst sequence stimulation of the vagus nerve [9]. Meanwhile an important manifestation of burst stimulation of the vagus nerve is the synchronization of the cardiac and vagal rhythms which arises under these conditions, shown by the fact that the heart responds to each burst of impulses applied to the nerve by a separate contraction [10, 12]. Measurement of the burst sequence frequency within the limits of a definite range is reproduced synchronously by the heart, making controlled bradycardia possible [3]. Its existence is evidence that parasympathetic regulation is not confined to its purely inhibitory tonic action, manifested as slowing of the heart beat or even cardiac arrest, but it also presupposes the possibility of cyclic synchronizing influences, responsible for the phenomenon of a controlled cardiac rhythm. The mechanisms of cyclic vagal control of the cardiac rhythm has still received only little study. It can be tentatively suggested that a definite role in its origin is played by the modulating influence of peptides secreted together with acetylcholine in response to burst stimulation of the vagus nerve.

In this investigation we studied the effect of somatostatin, as a possible co-transmitter [7, 9], on the structure of the vagal chronotropic effect during burst stimulation of the vagus nerve.

EXPERIMENTAL METHOD

Experiments were carried out on 11 adult noninbred cats, male and female. The animals were anesthetized intraperitoneally with a mixture of chloralose and pentobarbital (75 and 15 mg/kg respectively) and artificially ventilated. The right vagus nerve was divided in the neck in the region of the thyroid cartilage, and its peripheral end was placed on bipolar platinum electrodes and immersed in a melted mixture of wax and mineral oil. The right vagus nerve was stimulated by volleys of square pulses from an ÉSU-2 electrostimulator. Volleys of 3, 6, and 9 pulses were used. The duration of the pulses and frequency of generation of pulses in the volley were 2 msec and 40 Hz respectively, and the amplitude was equal to 5-6 times the threshold value. The electrogram of the right atrium was derived by means of a unipolar probe, introduced through the femoral vein, and ÉKPSChT-4 electrocardiograph and recorded on and N 338-4 automatic writer. Intervalograms of cardiac contractions were recorded by means of an interference-free intervalometer. The magnitude of the vagal chronotropic effect and of its individual components (chronic and synchronizing) was calculated. The abundance of the latter effect was estimated from the width of the ranges of the heart rate. The magnitude of the tonic component was found as the difference between the original heart rate

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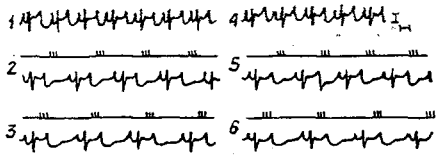

Fig. 1

Fig. 2

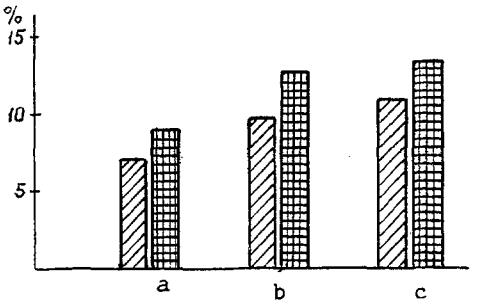

Fig. 3

Fig. 1. Effect of somatostatin on synchronization of cardiac and vagal rhythms (stimulation by bursts of three pulses). 1 and 4) Initial heart rate before and after injection of somatostatin respectively; 2 and 3) upper and lower limits of synchronization range respectively; 5 and 6) the same after injection of somatostatin Calibration, 1 mV, 0.1 sec.

Fig. 2. Effect of somatostatin on initial HR (intervalogram). Arrow indicates time of injection of peptide.

Fig. 3. Effect of somatostatin on magnitude of synchronizing component of vagal chronotropic effect. a, b, c) Stimulation of vagus nerve by bursts of 3, 6, and 9 pulses respectively. Columns indicate magnitude of synchronizing component (in % of initial HR.) With all conditions of stimulation, first column represents initial value, second column value after injection of peptide.

(HR) and HR at the upper (relative to the original cardiac rhythm) boundary of the synchronization range. The total magnitude of the vagal chronotropic effect was found as the sum of its components, Somatostatin (from "Boehringer Mannheim," Germany, SRIF-14) was injected intravenously by jet infusion in 0.5 ml physiological saline and in a dose of 10^{-8}-10^{-9} M. The results were subjected to statistical analysis by the direct difference method [1].

EXPERIMENTAL RESULTS

In response to burst stimulation of the vagus nerve ranges of control of the cardiac rhythm were obtained, within which the heart responded by a single contraction to each burst of pulses (Fig. 1). The boundaries of the ranges of control of the cardiac rhythm are given in Table 1. Injection of somatostatin led to significant slowing of the spontaneous HR, which could be detected as early as during the first 1-2 min after injection of the peptide (Fig. 2). The degree of slowing of HR was 6.4% of its initial value. Vagus nerve stimulation, combined with the action of

TABLE 1. Effect of Somatostatin on Vagal Chronotropic Effect and Its Individual Components with Burst Stimulation of Vagus Nerve

Dose of peptide	Initial HR	Power of burst	Boundary of synchronization range		Synchronizing component	Tonic component	Vagal chronotropic effect
			upper	lower			
0	194,3±4,5	3	118,7±3,1	105,0±4,1	13,7±1,5	75,6±5,5	89,3±5,9
		6	103,5±3,4	84,6±4,3	18,9±3,1	90,8±3,7	109,7±11,3
		9	91,5±5,3	69,7±2,4	21,8±2,3	102,8±5,8	124,6±8,3
		3	119,1±3,0	102,4±2,9	16,7±1,6	62,8±6,2	79,5±6,9
10^{-8}—10^{-9}	181,9±6,4	6	105,0±3,5	81,9±3,1	23,1±2,2	76,9±4,2	100,0±6,3
		9	92,6±2,8	68,1±2,0	24,5±2,7	89,3±5,5	113,8±9,6

Legend. For all parameters studied, $p < 0.05$.

somatostatin, became less effective, as shown by reduction of the vagal chronotropic effect of all conditions of stimulation (Table 1). Inhibition of the vagal chronotropic effect with stimulation by 3, 6, and 9 pulses amounted to 10.9, 8.8, and 8.7% respectively. In all cases inhibition of the vagal chronotropic effect was due to weakening of the tonic component by 16.9, 15.3, and 13.1% respectively of the original value.

The factor determining the character of the effect of somatostatin on cyclic vagal control of the cardiac rhythm is the increase in the synchronizing component of the vagal chronotropic effect (Table 1), observed under these conditions. This effect was manifested as widening of the ranges of control of the cardiac rhythm, which amounted to 21.9, 22.2, and 12.4% respectively with stimulation by 3, 6, and 9 pulses. The quantitative trend of the cyclic synchronizing influences, expressed as relative numbers, also was characterized by an increase. For instance, whereas the initial value of the ranges of control of the cardiac rhythm with stimulation of the type described above amounted to 7.1, 9.7, and 11.2% respectively of the spontaneous HR, after injection of the peptide, the same parameters had values of 9.2, 12.7, and 13.5% (Fig 3).

Incidentally, the action of somatostatin on the magnitude of vagal synchronizing influences depended to some degree on the initial value of the ranges of control of the cardiac rhythm. For instance, in three of 11 experiments the potentiating effect was absent, evidently due to the initially high value of the ranges of control of the cardiac rhythm. This was usually observed in cases when the initial value of the latter, in response to stimulation by three pulses exceeded 18-20 beats, whereas with stimulation by six and nine pulses, the excess was 25-30 beats. This distinguishing feature in this case was evidently the result of the predominantly "normalizing" character of their action, characteristic of regulatory peptides, and aimed at stabilizing this parameter within the range of physiologically acceptable fluctuations [5].

The action of the peptide was preserved for 30-40 min, after which all the parameters gradually returned toward their original level.

The inhibitory effect of somatostatin which we observed on the initial HR is in agreement with data in the literature on this question [8, 11, 13]. The results may also be of some interest in connection with the further development of our ideas on mediator mechanisms of the vagal effect on cardiac rhythm. The magnitude of the tonic component of the vagal chronotropic effect has been shown to depend essentially on the acting acetylcholine concentration [2]. At the same time, changes in the latter do not lead to a complementary change in the magnitude of the cyclic synchronizing influences. Accordingly, the potentiating action of somatostatin relative to vagus-controlled bradycardia would seem to be evidence of a combined role for acetylcholine-dependent and peptidergic mechanisms in the realization of the vagal effect on cardiac rhythm when the vagus nerve is subjected to burst stimulation

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EFFICACY OF ARTIFICIAL VENTILATION IN OIL MICROEMBOLISM AND SUBSEQUENT PULMONARY EDEMA

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One of the causes of pulmonary edema (PE) is embolism of the lungs, including the fat embolism which arises as a result of the entry of yellow bone marrow into the blood stream after fractures of the long bones. When a model of fat-induced edema is created in order to study the mechanisms of onset of the condition and to develop adequate methods of diagnosis and correction, intravenous injection of olive oil is usually used, for this substance closely resembles yellow bone marrow in its content of saturated and unsaturated fatty acids [2]. The combination of therapeutic measures used in the treatment of patients with PE is artificial ventilation of the lungs (AVL).

The aim of this investigation was to study activity of the cardiovascular and respiratory systems in experimental oil microembolism of the lungs (MEL) and to evaluate the efficacy of AVL.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred cats, male and female, weighing 2-4 kg, under pentobarbital anesthesia (35 mg/kg, intraperitoneally). The animals' rectal temperature was measured and was maintained at the initial level with the aid of an electric heater, with an accuracy of 0.5°C. Tracheotomy was performed at the level of one third of the trachea, and the systemic blood pressure (BP) was recorded through a cannula introduced into the femoral artery. In the course of the experiment the following parameters were determined with the aid of an MKh-01 polygraph, made in the former USSR: systemic HP, heart rate (HR), respiration rate (RR), and respiratory minute volume (RMV). Values of the partial pressure of oxygen in the arterial blood (p_aO_2) and its reaction (pH_a) were recorded continuously by means of a DS 67101 continuous flow cuvette, the temperature which was kept at 37.5°C

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