Modulatory Effect of Neurotensin on Parasympathetic Regulation of the Heart Rhythm

O. E. Osadchii, V. M. Pokrovskii, and A. N. Kurzanov

UDC 612.172.2+612.819.91

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 115, № 5, pp. 453–455, May, 1993
Original article submitted December 22, 1992

Key Words: *vagus; burst stimulation; control of cardiac rhythm; neurotensin*

Experimental modeling of the vagal natural impulse activity synchronized with the pulus provides the possibility for cycle-by-cycle control of the cardiac rhythm [2]. The latter becomes possible due to the fact that any change in the repetition rate of the bursts delivered to the vagus nerve within a certain range is precisely reproduced by the heart. It is thus assumed that in addition to the purely tonic inhibitory effect resulting in bradycardia, the functional structure of the vagus control of the heart rhythm also includes the so-called synchronizing component, through which the control of the heart rhythm against the backgroung of bradycardia is accomplished [5]. Previously we demonstrated that the functional direction of the vagal regulation of the rhythmogenic heart structures is determined to a great extent by pecularities of the humoral-transmitter component of the parasympathetic regulatory system, in particular, by the interaction between acetylcholine and regulatory peptides [3,4] within the latter.

In the present study the dynamics of the functional structure of the vagal chronotropic effect in response to neurotensin, a peptide involved in peripheral influences on the pacemaker [6-8], is investigated.

MATERIALS AND METHODS

The experiments were carried out on 8 adult male and female cats. The animals were anesthetized by intraperitoneal injection with a chloralose-nembutal mixture (75 and 15 mg/kg, respectively) and artificially ventilated. The right vagus nerve was divided in the neck near the thyroid cartilage. The peripheral end of the nerve was pinned onto bipolar platinum electrodes and fixed with a mixture of melted wax and mineral oil. The stimulation of the right vagus nerve was performed with an ESU-2 electro-

TABLE 1. Effect of Neurotensin on Vagal Chronotropic Effect and Its Components

Original HR	Number of pulses in burst	Limits of Synchronization range		Synchronization component	Tonic component	Vagal chronotropic effect
		upper	lower			
184.6±9.3	3	112.1±3.7	93.1±3.9	19.0±2.8	72.5±8.9	91.5±9.4
		122.5±5.2	103.0±5.9	19.5±2.2	95.5±8.2*	115.0±9.3*
	6	100.1±3.9	77.3±2.0	22.8±3.3	84.5±9.7	107.3±9.0
		110.3±4.0	86.1±5.7	24.2±2.7*	107.7±9.2*	131.9±9.6*
218.0±9.8*		92.8±3.4	68.0±2.7	24.8±2.4	91.8±9.6	116.6±9.2
	9	102.8±5.3	78.0±5.0	24.8±1.7	115.2±9.2*	140.0±8.5*

Note. For each index: upper row denotes original value, lower row denotes value after injection of neurotensin. Asretisk: $p<0.02$.

Department of Normal Phisiology, Kuban' Red Army Medical Institute, Krasnodar. (Presented by B. I. Tkachenko, Member of the Russian Academy of Medical Sciences)

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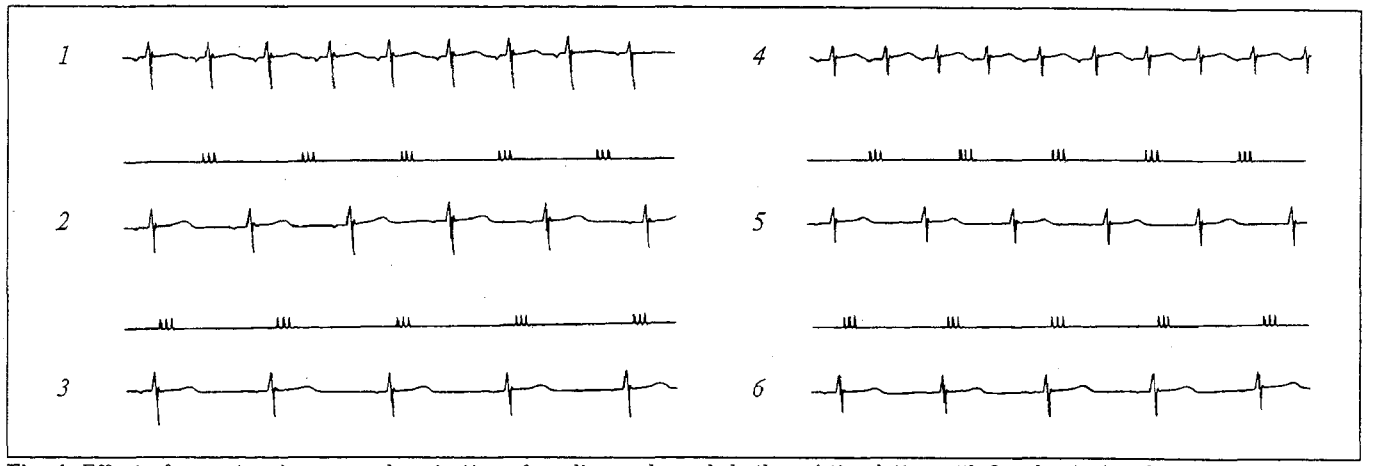

Fig. 1 Effect of neurotensin on synchronization of cardiac and vagal rhythms (stimulation with 3 pulses). *1* and *4*) initial HR before and after injection of peptide; *2* and *3*) upper and lower limits (respectively) of range of heart rate control, *5* and *6*) the same after injection of neurotensin. Calibration: 1 mV, 0.5 sec.

stimulator, using bursts of square pulses. Bursts of 3, 6, and 9 pulses were used. The duration and frequency of the pulses in a burst were 2 msec and 40 Hz, respectively; the amplitude was 5-6 threshold values. The ECG of the right atrium was recorded by means of a bipolar probe, inserted through the femoral artery, with an EKPCChT-4 electrocardiograph and H338-4 automatic writing device. The intervalogram of the heart cycle was recorded by means of an interference-proof device. The values of the chronotropic effect of the vagus as well as its tonic and synchronizing components were calculated. The contribution of the latter was estimated from the width of the range of heart rate control. The contribution of the tonic component was calculated as the difference between the original heart rate (HR) and the HR corresponding to the highest limit of synchronization. The total magnitude of the vagal chronotropic effect was found as the sum of these two components. Neurotensin (Boehringer Mannheim, Germany) (4×10^{-8} M) was infused intravenously in a volum of 0.2 ml phisiological saline. The data were subjected to statistical processing by the method of direct differences [1].

RESULTS

The stimulation of the vagus nerve led to bradycardia, which depended heavily on the cardiac cycle phase when the stimulus was delivered to the nerve (Fig. 1). Within a range restricted by sertain minimal and maximal values of possible reduction of the heart rate, a variations in the following frequency of bursts were synchronously reproduced by the heart, thus allowing for controlled bradycardia. The boundaries of the range of HR control are presented in Table 1. Neurotensin induced an increase of HR accompanied by a reduction of ECG voltage in 3 out of 8 cases. A decrease of cardiac cycle duration was noted as soon as 30 sec after injection of the peptide. However, the overall duration of tachycardia did not exceed 3-4 min (Fig. 2). The HR was increased by 18.1% as compared with the initial value.

The stimulation of the vagus nerve on the background of neurotropin injection was more effective, which manifested itself as a potentiation of the vagal chronotropic effect in all stimulation modes (Table 1). The vagal chronotropic effect for stimulation with 3, 6, and 9 pulses increased by 25.7, 22.9, and 20.1%, respectively. In all cases this effect was due to an increase in the tonic component by 31.7, 27,5 and 25.5%, respectively. The value of the synchronizing component, which is responsible for controlled bradycardia, did not change.

As applied to the "HR control" phenomenon, the effect of neurotensin manifested itself as a modulation of the susceptibility of the heart to vagal regulatory signals (Fig. 3). After injection of the peptide, there was a shift of the ranges of HR control in the upward direction along the frequency scale. For example, the initial boundaries of the rhythm control range during stimulation of the vagus nerve with 3, 6, and 9 pulses were 112.1±3.7 and 68.0±2.7 beats/min, whereas after the injection of neurotensin these parameters amoun-

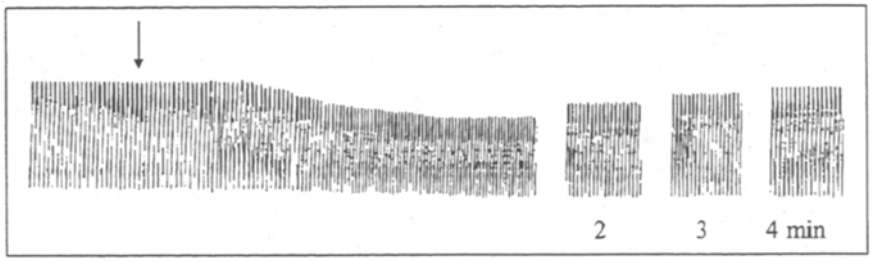

Fig. 2 Effect of neurotensin on original heart rate. Arrow: time of injection. Marks under the intervalogram: time after injection.

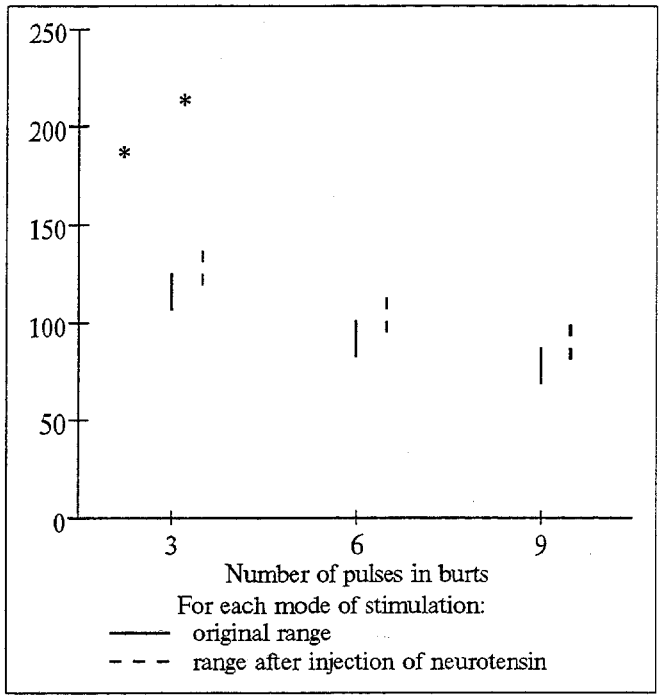

Fig. 3 Variation of ranges of controlled bradycardia after injection of neurotensin. Asterisk: HR before and after injection.

ted to 122±5.2 and 78.0±5.0 beats/min. The absolute value of the total range of HR control did not change.

The data obtained on the accelerating influence of neurotensin on HR are in conformity with other studies, performed on guinea pigs and rats [6-8]. On this basis it can be assumed that in the peripheral regulation of the heart neurotensin serves as a stimulatory peptide, increasing the baseline frequency of autonomic excitation of the pacemaker and, through this mechanism, its susceptibility to vagal influence. When comparing these data with our previous results concerning the negative chronotropic and vagolytic effect of somatostatin [4], we may conclude that there are broad possibilities of the peptidergic component in the modulation of parasympathetic regulatory influences on the heart. However, the selectivity of the vagotropic effect of regulatory peptides remains in all cases a common feature of their action, which is evidently essential for the relatively independent realization of functionally dissimilar parasympathetic influences on the pacemaker.

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