PEPTIDERGIC MODULATION OF THE VAGAL EFFECT ON THE CARDIAC RHYTHM

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

UDC 612.172.2+612.819.91

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

Parasympathetic control of the cardiac rhythm is not simply a purely inhibitory tonic action [3]. During vagus nerve stimulation by bursts of pulses, a lasting synchronization of cardiac and vagus rhythms takes place [7, 8]. The change in following frequency of the bursts, within a certain range, is reproduced synchronously by the heart, so that controlled bradycardia becomes possible [4]. Thus besides the tonic effect known previously, the vagal chronotropic effect also includes a so-called synchronizing component. One of the mechanisms responsible for the complex heterogeneous character of vagal chronotropic action may perhaps be the involvement of neuropeptides in the realization of parasympathetic influences on the cardiac rhythm [6, 9].

The aim of this investigation was to study the effect of peptides dalargin and secretin on the structure of the vagal chronotropic effect during burst stimulation of the vagus nerve.

EXPERIMENTAL METHOD

Experiments were carried out on 20 adult noninbred male and female cats. 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 with interelectrode distance of 2 mm, and irrigated with a warm mixture of wax and mineral oil. The right vagus nerve was stimulated by means of an ÉSU-2 electrostimulator with bursts of square pulses. Bursts of 3, 6, and 9 pulses were used. The duration of the pulse and frequency of its generation in the volley 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 unipolar probe, introduced through the femoral vein, and an ÉKPSChT-4 electrocardiograph, connected to an N338-4 automatic writer. The magnitude of the vagal chronotropic effect and its components (tonic and synchronizing) was calculated. The abundance of the latter was estimated 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 original heart rate (HR) and HR at the upper (relative to the initial rate) limit of the synchronization range. The total vagal chronotropic effect was found as the sum of the components. Dalargin (synthesized at the Laboratory of Peptide Synthesis, All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR) and secretin (from Sigma, USA) were injected intravenously by continuous infusion in 1 ml of physiological saline, in doses of 40 μg/kg and 1 μg/kg respectively. The results were subjected to statistical analysis by the direct differences method [2].

EXPERIMENTAL RESULTS

During the experiments ranges of synchronization within which the heart responded to each burst of pulses by a single contraction were regularly obtained (Fig. 1). Injection of dalargin (n = 10) led to weakening of the vagal chronotropic effect (Table 1), by amounts of 16.3%, 8.5%, and 7.8% respectively after stimulation by 3, 6, and 9 pulses. The inhibitory

Department of Normal Physiology, Kuban Red Army Medical Institute, Krasnodar. (Presented by Academician of the Academy of Medical Sciences of the USSR B. N. Tkachenko.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 112, No. 12, pp. 565-567, December, 1991. Original article submitted May 20, 1991.

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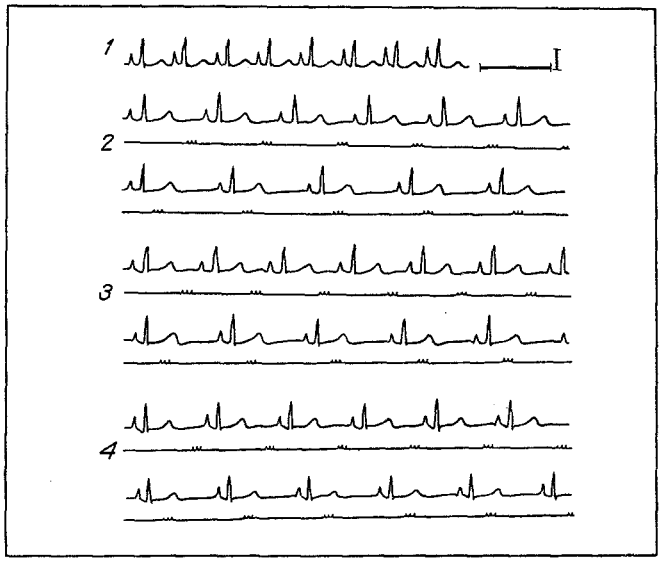

Fig. 1. Effect of dalargin and secretin on synchronization of cardiac and vagus rhythms (stimulation by burst of three pulses). 1) Initial heart rate, 2) heart rate at upper and lower limits of synchronization range, 3, 4) the same, under the influence of dalargin and secretin respectively. Calibration: 1 mV, 0.5 sec.

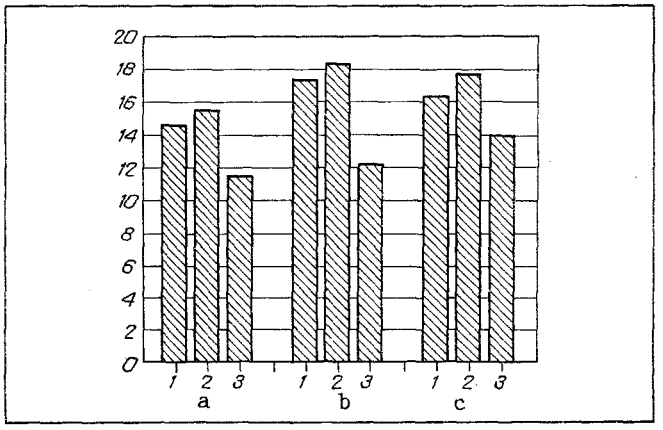

Fig. 2. Effect of dalargin and secretin on relative magnitude of synchronizing component of vagal chronotropic effect: a, b, c) stimulation by bursts of 3, 6, and 9 pulses respectively. With each mode of stimulation: column 1) average value (n = 20) of original synchronizing component (in % of overall vagal chronotropic effect), columns 2 and 3) the same, after injection of dalargin and secretin respectively.

effect was realized through reduction of the tonic component by 17.8%, 11.2%, and 9.9% respectively, which led to a shift of the ranges of heart rate control in the upward direction along the frequency shale, with no change in their absolute value. Meanwhile, in view of inhibition of the overall vagal chronotropic effect, there was an increase in the relative contributions of the synchronizing influences composing it (Fig. 2). For instance, the initial value of the synchronizing component during stimulation by 3, 6, and 9 pulses amounted to 14.0%, 15.9%, and 16.0% of the vagal chronotropic effect respectively. After injection of dalargin, the corresponding values of this parameter were 15.5%, 18.4%, and 17.8%. This

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

Number of pulses	Heart rate	Boundary of synchronization range		Synchronizing component	Tonic component	Chronotropic effect
		upper	lower			
3	195,1±7,4	115,0±4,5	102,0±5,3	13,0±1,7	80,1±6,3	93,1±7,4
	191,4±7,9	126,0±4,7	114,0±5,3	12,0±1,7	65,4±6,5*	77,4±7,2*
6	197,2±7,8	105,6±4,2	88,3±5,5	17,3±2,4	91,6±10,8	108,9±10,7
	194,0±7,0	112,9±4,6	94,6±5,4	18,3±2,7	81,1±10,9*	99,4±11,6*
9	194,3±10,3	96,0±3,7	77,3±3,4	18,7±2,3	98,3±9,8	117,0±9,2
	189,7±11,9	101,1±3,8	81,9±3,1	19,2±2,1	88,6±9,3*	107,8±9,6*

Legend. Here and in Table 2, for all modes of stimulation top line indicates initial values, bottom line values after injection of peptide; *$p < 0.05$.

TABLE 2. Effect of Secretin on Vagal Chronotropic Effect and Its Components

Number of pulses	Heart rate	Boundary of synchronization range		Synchronizing component	Tonic component	Chronotropic effect
		upper	lower			
3	196,0±7,0	118,6±5,0	104,1±5,5	14,5±2,1	77,4±7,2	91,9±7,1
	204,8±8,9	130,1±5,3	120,4±6,3	9,7±1,6*	74,7±6,1	84,4±6,5*
6	194,3±6,5	106,1±2,7	88,1±4,4	18,0±2,4	88,2±7,1	106,2±6,8
	199,3±8,2	113,6±5,8	101,6±8,8	12,0±3,5*	85,7±8,9	97,7±9,9*
9	193,6±9,5	99,2±4,4	79,8±4,7	19,4±4,1	94,4±8,1	113,8±5,6
	193,6±10,4	105,2±6,9	90,6±10,5	14,6±4,7*	88,4±9,5	103,0±8,8*

fact must evidently be taken into account when the therapeutic action of dalargin is evaluated in certain types of arrhythmias [1]. On the whole, the action of dalargin was short, not more than 3-4 min in duration, which is attributable to the pharmacokinetics of this peptide [5].

The action of secretin on vagus regulation of the heart rate, which was studied in two series of experiments ($n = 10$), also was inhibitory in character (Table 2). Weakening of the vagal chronotropic effect during stimulation by these modes amounted to 8.8%, 8.0%, and 9.5% respectively. In this case, however, the inhibitory effect was due to weakening of the synchronizing component, which led to a reduction of the ranges of heart rate control by 33.1%, 33.3%, and 24.7% respectively. The quantitative time course of the relative value of the synchronizing component also showed a decrease (Fig. 2). The reduction in the relative contribution of the latter to the overall vagal chronotropic effect in response to stimulation by 3, 6, and 9 pulses amounted in this case to 4.3%, 4.6%, and 2.8% respectively. The tonic component showed no significant change. The action of the peptide was long-lasting, more than 1 h after injection.

When the action of dalargin and secretin is compared, the inhibitory effect on vagal regulation of the heart rate in both cases, it will be noted, was realized through isolated inhibition of only one of the components of the vagal chronotropic effect. This may probably indicate the existence of selective peptidergic modulation of the vagus effect on the heart rate. In turn, the existence of independent regulation for each component of the vagal chronotropic effect may indicate differences in their physiological role in the regulation of cardiac activity associated with involvement of the parasympathetic system.

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