Effect of Neurotensin and Epinephrine on Sinus Arrhythmia Caused by Burst Stimulation of the Vagus Nerve

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Administration of neurotensin against the background of sinus arrhythmia caused by burst stimulation of the vagus nerve in cats restores synchronization of the cardiac and vagal rhythms or modulates the proportion between them. This either stops the arrhythmia or changes its parameters. The effects of the peptide are similar to those of epinephrine and are abolished by β-adrenoreceptor blockage.

Key Words: *vagus nerve; sinus arrhythmia; neurotensin; epinephrine*

The effect of the vagus nerve (VN) on the heart is modulated by peptides localized in neurons of the intracardial nervous system [2,9]. For instance, neurotensin (NT) considerably changes the dynamics of controlled bradycardia caused by synchronization of the cardiac rhythm with the frequency of bursts delivered to the VN [3]. The aim of the present study was to investigate the effect of this peptide under conditions of desynchronization of the vagal and cardiac rhythms, in particular in sinus arrhythmia [4].

MATERIALS AND METHODS

Experiments were carried out on 22 cats weighing 2.5-3.5 kg narcotized intraperitoneally with a Chloralose-Nembutal mixture (75 and 15 mg/kg, respectively), and artificially ventilated. The right VN was divided in the neck and its peripheral end was stimulated by bursts of 6 square pulses. The duration and frequency of the pulses in a burst were 2 msec and 40 Hz; the amplitude was 5-6 threshold values. The amplified ECG was recorded by means of a unipolar probe inserted through the femoral vein into the right atrium; the *P* wave of the ECG triggers the recording the heart cycle intervalogram. Neurotensin (Boehringer Mannheim), [D-Trp^{11}]-neurotensin (Sigma) (both in a dose of 4×10^{-8} M), and epinephrine hydrochloride (0.5×10^{-8} M) were infused intravenously. The data were processed statistically using the method of direct differences [1].

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RESULTS

The duration of the cardiac cycle after dissection of the right VN was 329.4±9.8 msec. Stimulation of VN resulted in bradycardia; within a certain range of burst repetition rate (from 1.44±0.09 to 1.78±0.1 Hz) the heartbeats became synchronous with the vagal stimuli (Fig. 1) allowing for strictly controlled modulation of the cardiac cycle duration (from 557.1±15.4 to 694.3±18.2 msec). These limits were specified as the upper and lower boundaries of the synchronization interval. A repetition rate exceeding this interval led to desynchronization and development of sinus arrhythmia. Sinus arrhythmia arose from disturbed parallelism between the repetition rate of bursts delivered to VN and the lengthened heart rate, so that position of the vagal stimulus varied from cycle to cycle. For instance, in above-synchronization arrhythmia, the burst repetition rate exceeded the heart rate and the next vagal stimulus

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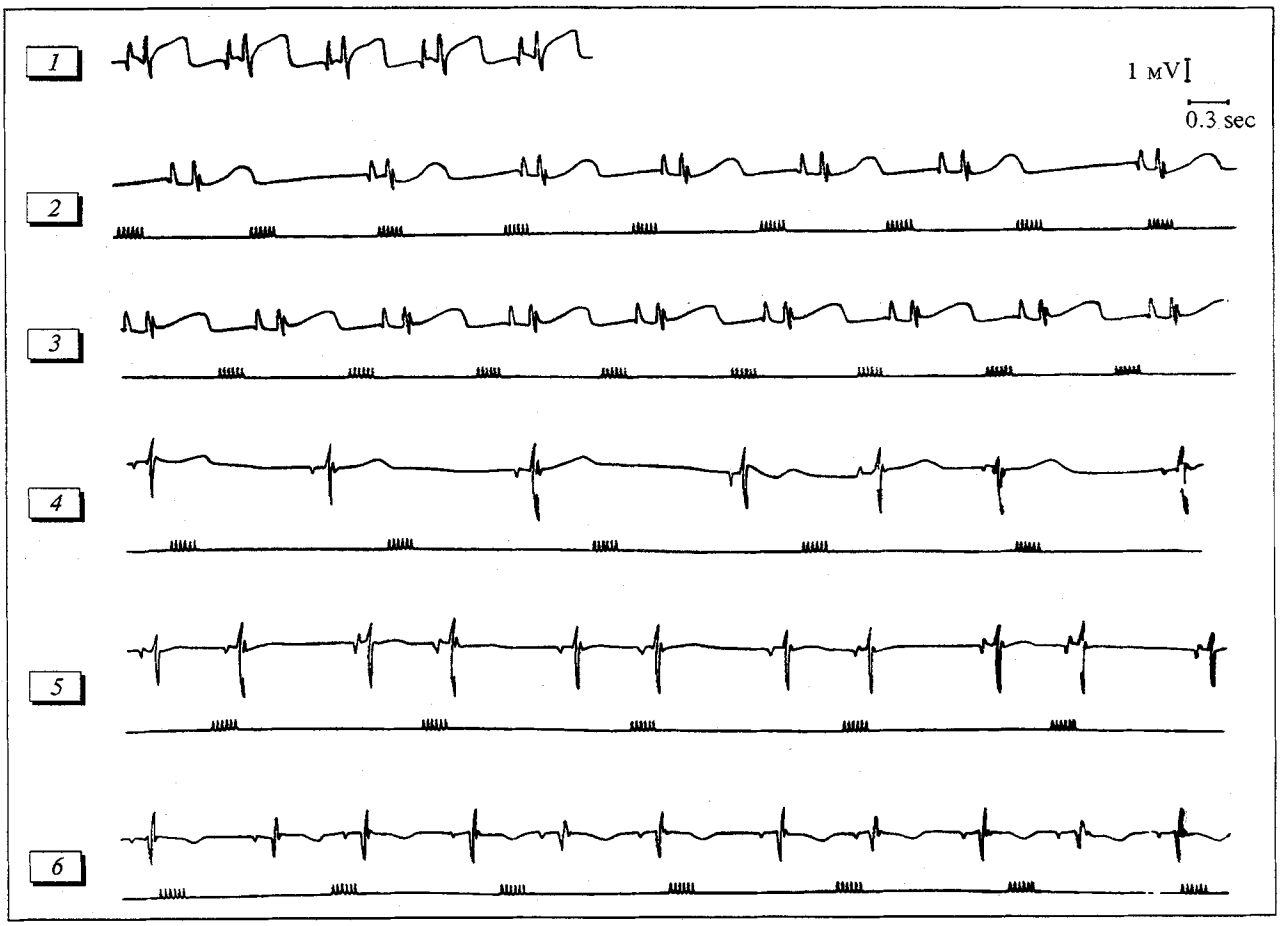

Fig. 1. Effect of neurotensin and epinephrine on the proportion between vagal and cardiac rhythms. *1*) initial heart rate; *2*) initial sinus arrhythmia above the upper limit of synchronization interval, proportion between vagal and cardiac rhythms is 7:6; *3*) resynchronization (1:1) after infusion of neurotensin; *4*) initial sinus arrhythmia below the lower limit of synchronization interval, proportion between vagal and cardiac rhythms is 5:6; *5*) sinus arrhythmia below the lower limit of synchronization interval after infusion of epinephrine, proportion between vagal and cardiac rhythms is 1:2; *6*) sinus arrhythmia below the lower limit of synchronization interval after infusion of neurotensin, proportion between vagal and cardiac rhythms is 2:3. In fragments 2-6: upper and lower records are ECG from the right atrium and artifact caused by stimulation of vagus nerve, respectively.

arrived at an earlier phase of the cardiac cycle (Fig. 1). By contrast, in the case of arrhythmia below the lower boundary of synchronization interval, stimulation rate was lower than the heart rate, and the next vagal stimulus arrived at a later phase of the cardiac cycle. In both cases, this cycle-by-cycle shift of the vagal stimulus modulated the chronotropic effect and resulted in periodic variations of *P—P* interval. Parameters of sinus arrhythmia are presented in Table 1. Infusion of NT (n=5) against the background of above-synchronization arrhythmia stopped arrhythmia (Fig. 2) and restored synchronization of the vagal and cardiac rhythms, the duration of cardiac cycle being 538.3±15.1 msec. Latency of the effect was 34.7±3.9 sec. A similar effect was produced by epinephrine (n=5); however, in this case synchronization was restored at a lower duration of the cardiac cycle (493.3±10.3 msec, p<0.01) and was characterized by a shorter latency (16.6±2.8 sec, p<0.01). In both cases the duration of cardiac cycle under conditions of synchronization was lower than minimal *P—P* interval in arrhythmia (Table 1), which implies an accelerating effect of the test preparations.

In the case of arrhythmia below the lower boundary of synchronization interval, infusion of NT (n=7) reduced the duration of both the minimal and maximum *P—P* intervals, whereas the severity of arrhythmia evaluated from the difference between these values remained unchanged. A peculiar phenomenon was a decrease in the number of cardiac cycles constituting a period of arrhythmia after NT infusion (to 3-4 *vs.* 5-6 under initial conditions, Fig. 2). This can be attributed to the fact that the difference between relatively slow rhythm of vagal stimulation and accelerated heart rate rose due to the accelerating effect of the peptide. This results in a more pronounced cycle-by-cycle shift of the vagal stimulus and desynchronization of the vagal and

TABLE 1. Dynamics of Sinus Arrhythmia Caused by Burst Stimulation of the Vagus Nerve

Type of arrhythmia	Vagus burst repetition rate, Hz	*P—P* interval, msec		
		minimum	maximum	difference between minimum and maximum
Arrhythmia above the upper limit of synchronization interval	1.8±0.07	565.0±13.2	751.6±14.7	186.6±12.8
Arrhythmia below the lower limit of synchronization interval:				
initial	1.42±0.08	476.1±12.6	621.1±15.9	145.0±11.7
after infusion of NT	1.42±0.08	415.0±12.8	553.0±16.1	138.0±12.0
after infusion of epinephrine	1.42±0.08	361.7±11.5	449.2±13.7	87.5±11.2

Note. *$p<0.01$ compared with the initial values.

cardiac rhythms (the end of a single cycle of arrhythmia) occurred more rapidly. This changes the proportion between the vagal and cardiac rhythms. For instance, if under conditions of initial arrhythmia the proportion between the number of vagal bursts and heartbeats was 4:5, after NT infusion this ratio became 2:3 (Fig. 1). The total duration of single arrhythmia period decreased from 2.84±0.3 to 1.98± 0.2 sec ($p<0.02$). This tendency was even more pronounced after infusion of epinephrine ($n=6$) due to a considerable accelerating effect, as evidenced by the decrease in the duration of the minimum and maximum *P—P* intervals (Table 1). The duration of single arrhythmia period decreased to 0.8±0.07 sec; the proportion between vagal stimuli and heartbeats was 1:2. The arrhythmia thus consisted of alternating cardiac cycles with minimal and maximum durations (Fig. 1). It should be noted that vagal stimulation coincided with the shortest cardiac cycle, whereas the next cycle, despite the absence of VN stimulation, was longer. This was due to the fact that in cardiac cycles with minimal duration, the interval from vagal stimulus to subsequent depolarization of the atria did not exceed 100-150 msec, while the latency of chronotropic effect constituted 200-250 msec [5]. Therefore, the effect of vagal burst appeared during the next cardiac cycle and was responsible for its lengthening. A characteristic effect of epinephrine was alleviation of sinus arrhythmia (Table 1).

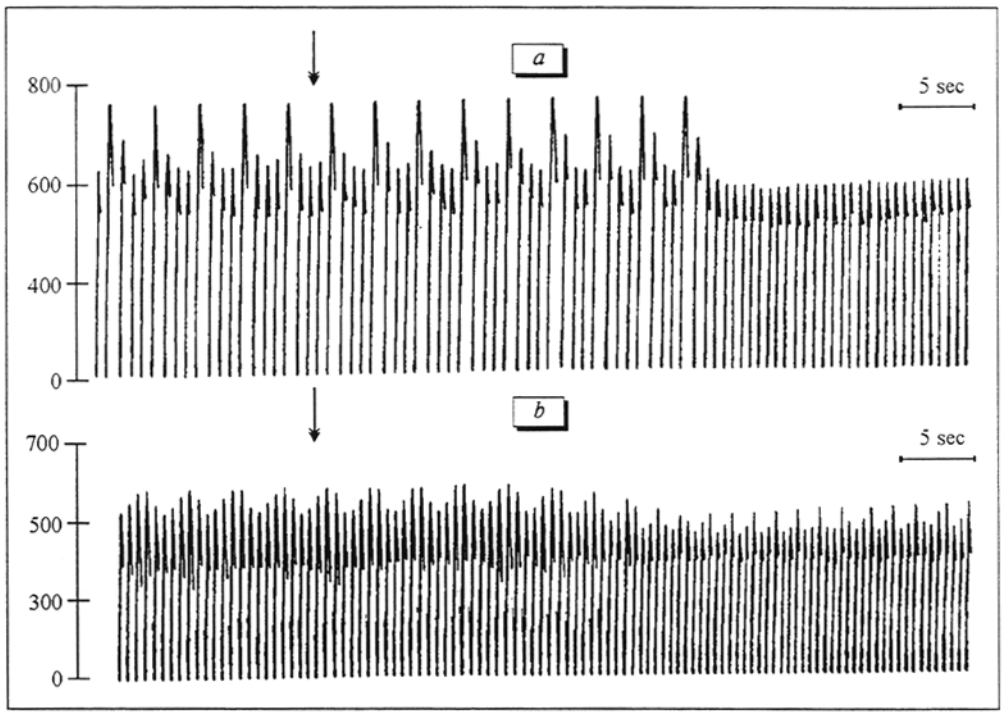

Fig. 2. Effect of neurotensin on the dynamics of vagal sinus arrhythmia. Arrhythmia outside the upper (*a*) and lower (*b*) limits of synchronization interval. Ordinate: *P—P* interval, msec. Peptide infusion is indicated by an arrow.

In 2 experiments, NT infusion in arrhythmia below the lower boundary of synchronization interval restored synchronization of vagal and cardiac rhythms. The latter was an unexpected phenomenon, since this effect could be achieved through aggravation of bradycardia and synchronization of heartbeats with relatively slow rhythm of vagal stimulation. However, the above-described dynamics can be explained on the basis of the assumption that the vagotropic effect of NT is mediated through stimulation of the release of endogenous catecholamines. This assumption arises from a longer latency of the effect of NT comparing to epinephrine and the absence of the effect against the background of β-adrenoreceptor blockage (1 mg/kg obsidan, intravenously, n=5). Mild sympathetic activation is known to enhance vagal influences on the heart [6]. This probably enables resynchronization at a relatively slow rate of vagal stimulation. More massive release of catecholamines was accompanied by a pronounced accelerating effect which determined typical changes in the dynamics of arrhythmia observed in the majority of the experiments.

The effect of NT was characterized by marked desensitization, i.e., no effect was observed in repeated infusion of NT. [D-Trp^{11}]-neurotensin (n=5) had no effect on the dynamics of sinus arrhythmia. This agrees with previous data that modification of the NT molecule by substituting 10-13 amino acid residues considerably reduces the peptide activity [7,8].

Our results suggest that NT can modulate the interaction between vagal and cardiac rhythms. This results in adaptation of the pacemaker to perception of accelerated vagal impulse activity or in changed proportion between vagal and cardiac rhythms. In the first case, the vagal influence is converted from arrhythmogenic into synchronizing, while in the second case we observed a change in the arrhythmia parameters.

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