Effect of Met-Enkephalin on Sinus Arrhythmia Caused by Burst Stimulation of the Vagus Nerve

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

UDC 612.172.2+612.819.91

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 116, № 7, pp. 4-6, July, 1993
Original article submitted February 19, 1993

Key Words: *vagus; burst stimulation; sinus arrhythmia; met-enkephalin*

Stimulation of the vagus nerve with bursts of pulses synchronized with each heartbeat provides the possibility for precise control of the cardiac rhythm [4]. The latter is accomplished due to the fact that any change in the repetition rate of the bursts within a certain range is synchronously reproduced by the heart, so that the vagal bradycardia observed under these conditions is controllable. A peculiarity of this phenomenon is the fact that beyond the above-mentioned boundaries of the repetition rate, burst stimulation leads to immediate desynchronization of the cardiac and vagal rhythms and to the development of sinus arrhythmia [5,6]. The antiarrhythmic effect of opioid peptides described in the literature has been established for arrhythmia caused by hyperactivation of the sympathetic nervous system [1,2]. At the same time, one of the aspects of the cardioprotective effect of opioid peptides can be assumed to be an inhibition of the arrhythmogenic influence of the vagus nerve with the simultaneous recovery of the synchronized perception of the regulatory influences from the central nervous system (CNS). The verification of this assumption regarding a member of the opioid family, met-enkephalin, was the objective of the present study.

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

MATERIALS AND METHODS

The experiments were carried out on 16 cats anesthetized intraperitoneally 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 and its peripheral end was pinned onto bipolar platinum electrodes. The right vagus was stimulated by means of an ESU-2 electrostimulator, using 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 electrogram of the right atrium was recorded by means of a bipolar probe inserted through the femoral artery. The intervalogram of the heart cycle (heart rate, HR) was recorded with an interference-proof intervalometer. The upper and lower boundaries (compared with the initial HR) of the synchronization interval, within which every stimulus delivered to the vagus caused a single heartbeat, were determined. Sinus arrhythmia was produced by the repetition rate of the bursts surpassing this interval. For this, the electrostimulator was adjusted in such a way as to establish a duration of the interburst interval 10-20 msec longer or, conversely, shorter than the lower and upper limits of the synchronization range. The arrhythmogenic effect of the vagus nerve was judged from the ratio between the minimal and maximal length of the cardiac cycle during arrhythmia [5].

0007-4888/93/0007-0759$12.50

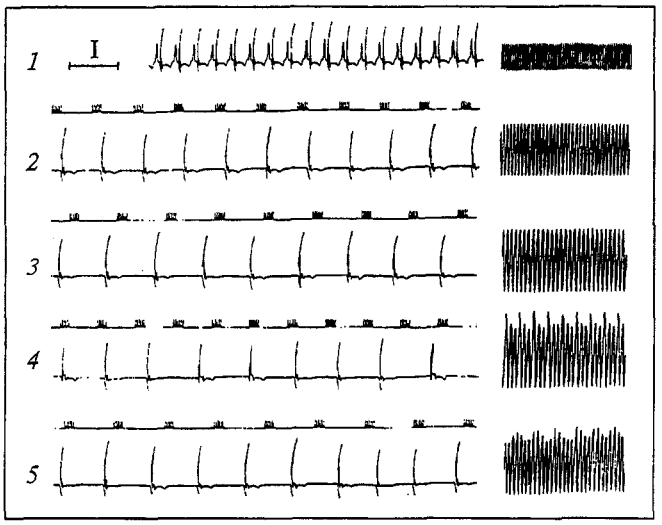

Fig. 1. Cardiac rhythm management and sinus arrhythmia caused by burst stimulation of the vagus nerve. *1*) original HR; *2*) upper boundary of controlled bradycardia; *3*) lower boundary of controlled bradycardia; *4*) sinus arrhythmia above upper boundary of controlled bradycardia; *5*) sinus arrhythmia below lower boundary of controlled bradycardia; at left: electrogram of right atrium and artefact from stimulation of vagus nerve; at right: intervalogram of heartbeats. Calibration: 1 mV, 0.5 sec.

Met-enkephalin (synthesized by I. V. Bobrova, Institute of Organic Synthesis, Latvian Academy of Sciences) was injected in a dose of 100 μg/kg in 1 ml of physiological saline. Naloxone (Sigma, USA) was injected intravenously in a dose of 1 mg/kg to block the opiate receptors. The data were subjected to statistical analysis by the method of direct differences [3].

RESULTS

Vagal bradycardia caused by burst stimulation of the vagus nerve depended considerably on the phase of the cardiac cycle during which the stimulus was delivered to the nerve (Fig. 1). Within a range restricted by a certain minimally and maximally possible lengthening of the cardiac cycle any change in the burst repetition rate was synchronously reproduced by the heart, thus allowing for controlled bradycardia. For an initial duration of the cardiac cycle of 324.3±7.6 msec, the upper and lower boundaries of the synchronization interval were 591.4±18.9 and 756.6±27.6 msec, respectively. A repetition rate exceeding this interval led to desynchronization of the vagal and cardiac rhythms and to the development of sinus arrhythmia, consisting of a regular periodic alternation of R-R intervals of different length (Fig. 1). The cardiac cycles were more frequent in the case of arrhythmia above the upper limit of the synchronization interval, which is attributed to a more frequent stimulation of the vagus nerve compared with that during arrhythmia below the lower limit of this interval.

The parameters of sinus arrhythmia are presented in Table 1.

In the case of upper-synchronization arrhythmia, injection of met-enkephalin (n=7) abolished arrhythmia and restored the synchronization of the cardiac and vagal rhythms as soon as after 10-20 sec (Fig. 2). The latter was evidently due to a changed sensitivity of the heart rhythmogenic structures to the vagal influence; as a result of this, the burst repetition rate, which initially produced an arrhythmogenic effect was precisely reproduced by the heart after peptide injection, with synchronization and the possibility of HR control being maintained. For restoration of the regular rhythm, the duration of the cardiac cycle was 556.4±18.2 msec. The above assumption is confirmed by the fact that sinus arrhythmia may also be induced against the background of met-enkephalin by further increasing the repetition rate of the bursts delivered to the vagus. For instance, sinus arrhythmia above the upper limit of synchronization arose for an interburst interval of 574.3±19.0 msec before and 540±019.2 msec after peptide injection. The latter points to an elevation of the heart's perception threshold of the vagal arrhythmogenic influence.

Compared to arrhythmia arising above the upper limit of controlled bradycardia, the desynchronization of the vagal and cardiac rhythms below the lower limit of that interval occurred at a much greater interburst interval, i.e., at a lower repetition rate of vagal stimulation, thus explaining some peculiarities of the antiarrhythmic effect

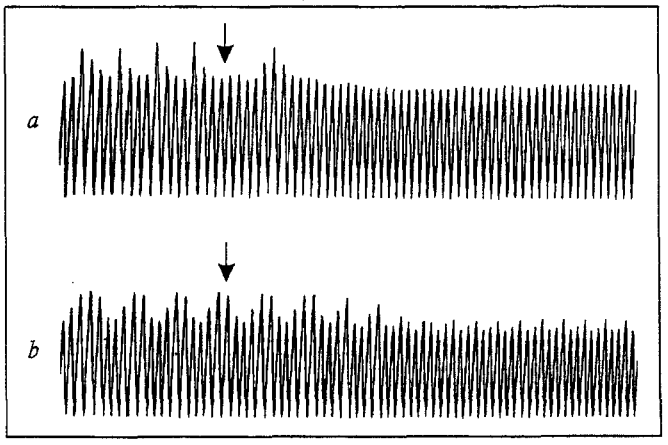

Fig. 2. Effect of met–enkephalin on sinus arrhythmia caused by burst stimulation of vagus nerve. *a,b*) effect of met–enkephalin on sinus arrhythmia outside upper and lower boundaries, respectively, of interval of synchronization of vagal and cardiac rhythms. Arrow indicates moment of peptide injection.

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

Parameter	Sinus arrhythmia	
	above upper boundary of synchronization interval	below lower boundary of synchronization interval
Length of interburs interval for vagal stimulation, msec	574.3±19.0	767.8±32.4
Mimimum length of cardiac cycle, msec	569.3±24.3	556.4±33.2
Maximum length of cardiac cycle, msec	764.3±45.6	744.2±20.1
Difference between minimum and maximum length of cardiac cycle	195.0±25.5	187.8±36.7

of met-enkephalin (n=7). The injection of peptide in two experiments completely abolished and in 5 others considerably reduced sinus arrhythmia (Fig. 2). After the injection of the peptide the maximal and minimal intervals in sinus arrhythmia were 472.0±25.0 and 546.0±27.1 msec, respectively, and the fluctuation of cardiac cycle length was 74.0±4.0 msec, which is reliably lower (p<0.02) than the initial values (Table 1). However, synchronization of the vagal and cardiac rhythms was not restored in this case. This is probably due to the vagolytic effect of the peptide, resulting in a reduced efficacy of parasympathetic influence on HR, so that pacing the heart slowly enough was impossible.

The above-described effect of met-enkephalin with respect to sinus arrhythmia outside the upper and lower boundaries of the synchronization interval was not abolished by preliminary injection of naloxone (n=4). Thus, the mechanism of this effect was not dependent on the activation of the opiate receptors and was likely due to the direct influence of met-enkephalin on the processes underlying cholinergic synaptic transmission.

The data obtained suggest a possible role of met-enkephalin in restricting the arrhythmogenic influence of the vagus nerve on the pacemaker, which manifests itself either in an increased susceptibility of the heart to high-frequency vagal impulse activity from the CNS or in a decreased efficacy of vagal stimulation on the pacemaker in the case of a low repetition rate of the stimulus. The effect of met-enkephalin reported here may be useful in different forms of discordance between the central and peripheral generators of the heart rhythm.

REFERENCES

1. Yu. B. Lishmanov, L. N. Maslov, and T. Yu. Rebrova, *Byull. Tomsk. Nauch. Tsentra, Akad. Med. Nauk SSSR*, № 3, 3 (1991).
2. F. Z. Meerson, M. G. Pshennikova, L. M. Belkina, *et al.*, *Khim. Farm. Zh.*, **23**, № 9, 1034 (1989).
3. E. V. Montsevichyute-Eringene, *Pat. Fiziol.*, № 4, 71 (1964).
4. V. M. Pokrovskii, *Fiziol. Zh. SSSR*, **74**, № 2, 259 (1988).
5. Yu. R. Sheikh-Zade and V. M. Pokrovskii, *Byull. Eksp. Biol.*, **99**, № 4, 393 (1985).
6. V. A. J. Slenter, J. J. Salata, and J. Jalife, *Circ. Res.*, **54**, № 4, 436 (1984).