Cardiotropic Effects of Met-Enkephalin and Somatostatin under Conditions of Neurotensin Receptor Blockade

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

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 130, No. 11, pp. 497-500, November, 2000
Original article submitted July 4, 2000

Pretreatment with the neurotensin receptor antagonist decreased the severity and time of Met-enkephalin-induced inhibition of vagal chronotropic effects in cats. The opiate receptor antagonist naloxone produced a delayed inhibitory effect on the synchronizing component of the vagal chronotropic effect under conditions of neurotensin receptor blockade. Cardiotropic effects of somatostatin remained unchanged during neurotensin receptor blockade. These data indicate one-way and two-way interactions between peptides modulating parasympathetic cardiac regulation.

Key Words: *neurotensin; Met-enkephalin; somatostatin; cardiac regulation*

Stimulation of cardiac branches of the vagus nerve (VN) induces the release of various neurotransmitters from the presynaptic terminals. The neurotransmitter cocktail includes not only acetylcholine, but also other colocalized regulatory peptides [5,6] modulating the effect of acetylcholine and, therefore, regulating vagal chronotropic effect (VCE) and the balance between its inhibitory tonic and synchronizing components [2,3]. This modulation results from close interaction of regulatory peptides, rather than from their independent effects. Our previous studies showed that Met-enkephalin (ME) potentiates the increase in the heart rate (HR) and vagal inhibitory tonic effect induced by neurotensin. By contrast, the effects of neurotensin are blocked during its combined use with somatostatin [4]. It is still unknown whether the cardiotropic effects of ME and somatostatin depend on endogenous neurotensin. Here we studied the modulatory effects of somatostatin, ME, and opiate receptor antagonist naloxone on the parasympathetic regulation of heart activity under conditions of neurotensin receptor blockade.

Department of Normal Physiology, Kuban Medical Academy, Krasnodar

MATERIALS AND METHODS

Experiments were performed on 55 rats weighing 2.5-3.5 kg and intraperitoneally narcotized with 75 mg/kg chloralose and 15 mg/kg nembutal. A unipolar probe for intracardiac ECG recording was introduced via the femoral vein into the right atrium. The length of cardiac cycle was estimated by R-R interval. The peripheral end of the right VN was stimulated with series of 3, 6, and 9 rectangular pulses using an ESU-2 electrical stimulator. The duration, frequency, and amplitude of stimulation were 2 msec, 40 Hz, and 5-6 thresholds, respectively. The effects of 1.3×10^{-8} M somatostatin, 10^{-7} M ME, and 0.2 mg/kg naloxone hydrochloride were studied 10-15 min after administration of the neurotensin receptor antagonist (3.1×10^{-8} M D-Trp^{11}-neurotensin). All preparations were dissolved in 0.5 ml physiological saline and infused intravenously. The results were analyzed by the method of direct differences [1].

RESULTS

Stimulation of VN caused bradycardia with synchronization of heart beats with the rhythm of vagal stimulation. The range of HR variations, within which this

0007-4888/00/0011-1038$25.00

phenomenon persisted, reflected the degree of VCE synchronizing component. The difference between the initial HR and cardiac rhythm at the upper limit of the synchronization range reflected the tonic component of VCE. The total VCE corresponded to the sum of its components (Table 1). The parasympathetic regulation of heart activity remained unchanged under conditions of neurotensin receptor blockade.

ME (n=10) decreased HR by 12.4% and inhibited VCE under conditions of 3-, 6-, and 9-pulse stimulation of VN by 32.8, 31.2, and 27.6% due to suppression of the tonic components by 34.6, 32.6, and 29.4%, respectively. These effects persisted for 30 min after peptide administration. Pretreatment with the neurotensin receptor antagonist (n=10) did not change the directionality of the vagotropic effects of ME, but decreased their degree and duration (Table 1). During 3-, 6-, and 9-pulse stimulation of VN, VCE was inhibited by 15.9, 14.7, and 16.3%, while its tonic components decreased by 16.0, 15.8, and 17.2%, respectively. These parameters returned to normal 15 min after ME administration.

ME produced a phasic synchronizing effect on vagal and cardiac rhythms short-term suppression followed by marked potentiation 15 min postinjection (Table 1). The dynamics of these effects did not change during neurotensin receptor blockade.

Opiate receptor blockade with naloxone (n=8) inhibited the synchronizing component of VCE during 3-, 6-, and 9-pulse stimulation of VN by 11.2, 14.6, and 13.0%, respectively. The initial HR, VCE, and its tonic component remained unchanged. After pretreatment with the neurotensin receptor antagonist (n=10), the synchronizing component of VCE decreased only 15-30 min after naloxone administration, which was accompanied by a decrease in the total VCE and its tonic component (Fig. 1).

Somatostatin (n=10) decreased HR by 7.7% and inhibited VCE and its tonic component by 8.6-16.9% (mean 12.3%) depending on the type of VN stimulation. At the same time, the synchronizing component increased by 21.9, 22.2, and 15.4% during 3-, 6-, and 9-pulse stimulation, respectively. The neurotensin receptor antagonist (n=7) did not change the dynamics of these effects.

Thus, one-way antagonistic interactions between neurotensin and somatostatin underlie their modulatory effects on parasympathetic cardiac regulation. Somatostatin blocks vagotropic effects of neurotensin

TABLE 1. Effects of ME on Synchronization of Vagal and Cardiac Rhythms (bpm) under Conditions of Neurotensin Receptor Blockade ($M\pm m$)

Parameter, number of pulses		Baseline	After administration of neurotensin receptor antagonist	After ME administration	15 minutes after ME administration
Initial HR		184.9±5.2	182.7±5.4	169.4±5.9*	178.5±5.5
Synchronization range					
upper limit	3	114.0±6.0	115.2±7.1	112.7±5.7	108.2±6.8
	6	104.8±5.1	106.6±5.6	105.3±5.7	101.3±5.9
	9	94.0±8.1	96.8±5.4	98.3±5.8	90.5±7.8
lower limit	3	100.4±6.2	103.0±8.1	102.4±5.2	92.3±6.8
	6	85.2±5.3	88.4±6.6	89.0±5.6	81.2±6.6
	9	72.9±7.8	76.1±6.1	80.2±6.1	68.4±5.8
Synchronizing component					
	3	13.6±0.8	12.2±1.6	10.3±1.1*	15.9±0.9
	6	19.6±1.4	18.2±1.0	16.3±1.0*	20.1±0.9
	9	21.1±1.6	20.7±1.8	18.1±1.3*	22.1±1.3
Tonic component					
	3	70.9±5.5	67.5±5.6	56.7±5.6*	70.3±5.8
	6	80.1±5.9	76.1±6.1	64.1±7.1*	77.2±6.9
	9	90.9±7.8	85.9±6.9	71.1±6.8*	88.0±6.7
Vagal chronotropic effect					
	3	84.5±7.3	79.7±6.7	67.0±6.7*	86.2±6.8
	6	99.7±7.3	94.3±7.2	80.4±7.5*	97.3±7.6
	9	112.0±9.9	106.6±9.6	89.2±6.1*	110.1±8.4

Note. *p<0.05 compared to the control.

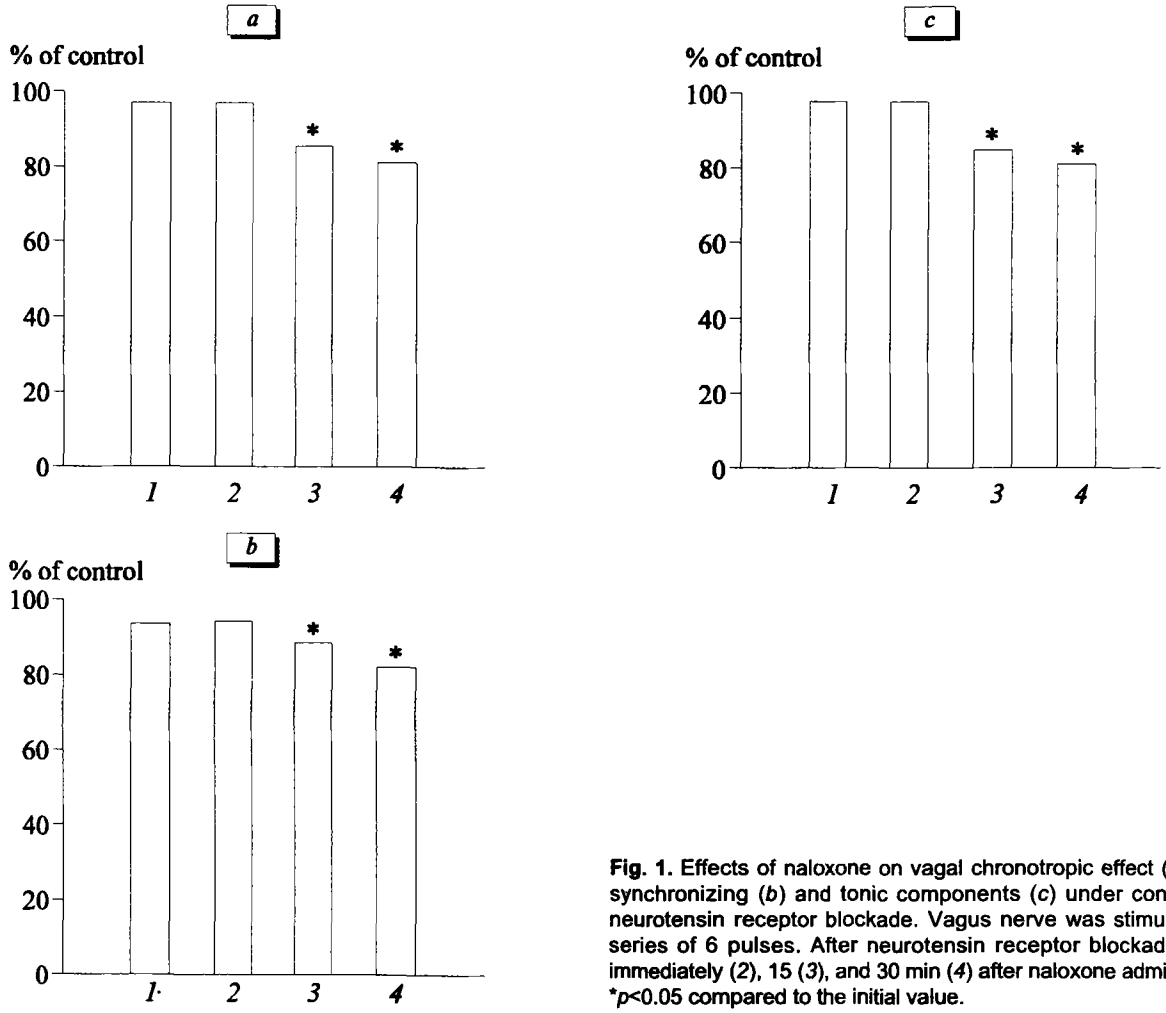

Fig. 1. Effects of naloxone on vagal chronotropic effect (*a*) and its synchronizing (*b*) and tonic components (*c*) under conditions of neurotensin receptor blockade. Vagus nerve was stimulated with series of 6 pulses. After neurotensin receptor blockade (*1*) and immediately (*2*), 15 (*3*), and 30 min (*4*) after naloxone administration. *$p<0.05$ compared to the initial value.

[4], but its modulatory action remains unchanged after neurotensin receptor blockade. At the same time, two-way peptide interactions are manifested in the modulatory effects of neurotensin and ME. ME potentiates cardiotropic effects of neurotensin [4], while neurotensin receptor blockade decreases the degree and duration of ME-induced suppression of inhibitory tonic action of VN. Under these conditions endogenous opiates produce a delayed effect on synchronization of the vagal and cardiac rhythms, which was confirmed by opiate receptor blockade with naloxone. Therefore, binding of endogenous neurotensin to its receptors is necessary for the realization of amplitude and temporal characteristics of the modulatory effects of ME on parasympathetic cardiac regulation. This positive influence is probably realized via plasma neurotensin in threshold concentrations. During combined action of exogenous neurotensin in high concentrations (10^{-8} M) and ME, cardiotropic effects of neurotensin increase and become dominant [4].

One-way and two-way peptide interactions constitute a possible mechanism responsible for the regulation of neurotransmitter systems modulating cardiac activity.

This work was supported by the Russian Foundation for Basic Research.

REFERENCES

1. E. V. Montsevichyute-Eringene, *Pat. Fiziol.*, No. 4, 71-78 (1964).
2. O. E. Osadchii and V. M. Pokrovskii, *Ros. Fiziol. Zh.*, **85**, No. 5, 628-636 (1999).
3. O. E. Osadchii and V. M. Pokrovskii, *Ibid.*, **85**, No. 8, 1051-1059 (1999).
4. O. E. Osadchii, V. M. Pokrovskii, and E. K. Totskaya, *Mechanisms of Functioning of Visceral Systems* [in Russian], St. Petersburg (1999), p. 243.
5. G. Campbell, I. L. Gibbins, J. L. Morris, *et al.*, *Neuroscience*, 7, No. 9, 2013-2023 (1982).
6. T. Hokfelt, *Neuron*, 7, 867-879 (1991).