Changes in Neuronal Pulse Activity of Bulbar Cardiovascular Center after Administration of Dynorphin A_{1-13}

S. D. Mikhailova, T. V. Vasil'eva, T. M. Semushkina, and G. I. Storozhakov

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Acute experiments on cats showed that dynorphin A_{1-13} modulates pulse activity of afferent neurons and interneurons in the bulbar cardiovascular center against the background of stable blood pressure.

Key Words: *dynorphin A_{1-13}; pulse activity; cardiovascular neurons; bulbar cardiovascular center; ischemic arrhythmias*

Our previous experiments showed that intravenous infusion of dynorphin A_{1-13} during myocardial ischemia decreases the severity of ischemic arrhythmias in cats with preserved innervation of the heart [2]. κ-Receptors (agonist dynorphin A_{1-13}) were found in brain regions involved in the central regulation of cardiovascular activity, including the cortex, hypothalamus, and medulla oblongata containing the bulbar cardiovascular center, which plays an important role in the development of myocardial ischemia [3-7].

Here we studied changes in pulse activity of afferent neurons (AN) and interneurons (IN) of the bulbar cardiovascular center after administration of dynorphin A_{1-13}.

MATERIALS AND METHODS

Experiments were performed on 56 male and female cats weighing 2.5-4.5 kg and anesthetized with nembutal (40 mg/kg intraperitoneally). Dynorphin A_{1-13} (Laboratory of Peptide Synthesis, All-Russia Research Center for Cardiology) was infused intravenously in a dose of 40 mg/kg.

Electrical activity of neurons was recorded in the nucleus tractus solitarius of the medulla oblongata (2 mm rostral and caudal to *obex*). Glass microelectrodes were filled with 2.5 M KCl (resistance 3-5 MΩ).

Simultaneously, ECG (lead II), pneumogram, and blood pressure in the femoral artery were recorded using a SR-41 magnetograph (Nihon Kohden). The signal were digitized using an analog-to-digital converter and processed using original Multisignal software.

Pulse activity of cardiovascular neurons was evaluated by firing rate, burst duration, and number of pulses per burst 30 sec and 1, 3, 5, 10, and 15 min after treatment. The neurons were considered to respond, if even one of these parameters differed from the baseline level or previous value. Functional type of neurons was determined by their initial activity as described previously [1].

The results were analyzed by Student's *t* test.

RESULTS

Pulse activity of 54 cardiovascular neurons (11 AN and 43 IN) was recorded.

First, the number of neurons responding to treatment in various periods of time (compared to the baseline level) was determined. Hemodynamic parameters remained unchanged (Table 1), while activity of 90% AN and 69% IN changed over the first 30 sec after

Russian State Medical University, Moscow

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TABLE 1. Blood Pressure and HR in Cats after Administration of Dynorphin A_{1-13} (*M*±*m*)

Parameter	Baseline level	Time after administration, min			
		0.5	1	3	15
Blood pressure, mm Hg					
systolic	128.0±6.3	131.6±6.4	132.8±6.0	129.6±5.5	126.0±8.4
diastolic	94.8±5.4	98.8±5.6	95.3±4.8	91.4±4.5	92.7±7.6
HR, bpm	119.4±4.7	116.8±4.8	124.4±5.0	121.8±5.3	119.6±7.8

treatment (Fig. 1). One minute after the start of infusion hemodynamic parameters remained unchanged, while pulse activity was modified in 100% AN and 91% IN. Three minutes after treatment hemodynamic parameters remained stable, while changes in activity were observed in 100% IN (Fig. 1).

Pulse activity of AN and IN decreased or increased at various terms of treatment, therefore changes in neuronal activity were compared with previous values. Thirty seconds after treatment firing rate decreased in 45% AN and 21% IN, and increased in 45% AN and 40% IN (Fig. 2). One minute after treatment the pulse rate increased in 37% IN and 12.5% AN, but decreased in 46% IN and 75% AN. Three, 5, 10, and 15 min after treatment pulse activity of AN and IN increased or decreased against the background of unchanged hemodynamic parameters (Table 1).

Our experiments show that pulse activity of neurons in the bulbar cardiovascular center changed over the first seconds after intravenous infusion of dynorphin A_{1-13}. It should be emphasized that pulse activity of AN and IN increased and decreased simultaneously (Fig. 2) and these changes were not accompanied by variations in blood pressure and heart rate (HR). These changes in the bulbar cardiovascular center can be associated not only with the direct effect of dynorphin A_{1-13} crossing the blood-brain barrier, but also with afferent information from receptors in the cardiovascular system [8]. Dynorphin A_{1-13} decreases the incidence of ischemic arrhythmias, which is probably related to changes in functional activity of the bulbar cardiovascular center playing an important role in the development of these disorders.

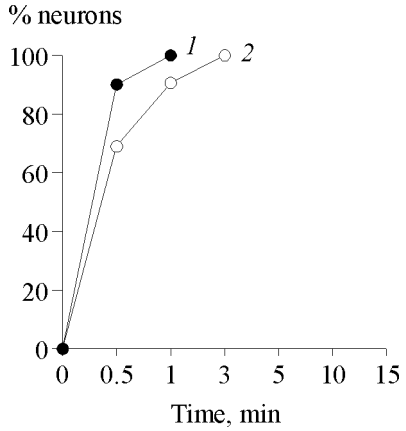

Fig. 1. Reaction of cardiovascular neurons to dynorphin A_{1-13} (compared to the baseline level). Here and in Fig. 2: afferent neurons (*1*) and interneurons (*2*).

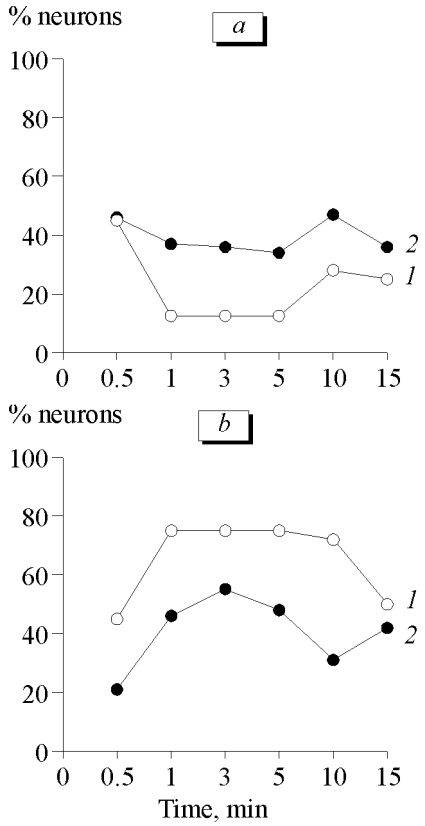

Fig. 2. Increase (*a*) and decrease (*b*) in pulse activity of cardiovascular neurons.

REFERENCES

1. S. D. Mikhailova, A. V. Kudinova, T. M. Semushkina, and G. I. Storozhakov, *Byull. Eksp. Biol. Med*., **125**, No. 3, 263-265 (1998).
2. S. D. Mikhailova, T. V. Vasil'eva, T. M. Semushkina, and G. I. Storozhakov, *Ibid*., **129**, No. 1, 34-37 (2000).
3. V. G. Smagin, V. A. Vinogradov, and S. A. Bulgakov, *Opiate Receptor Ligands* [in Russian], Moscow (1983).
4. M. Fodor, C. Pammer, and T. Gorcs, *J. Chem. Neuroanat*., **7**, No. 3, 141-157 (1994).

5. A. Goldstein and V. E. Ghazarossian, *Proc. Natl. Acad. Sci. USA*, **77**, No. 10, 6207-6210 (1980).
6. N. A. Sharif, E. Darie, A. D. Michel, and R. L. Whiting, *Brain Res*., **510**, No. 1, 108-114 (1990).
7. P. Slater, A. J. Gross, and L. Hewitt, *J. Recept. Res*., **9**, No. 2, 171-180 (1989).
8. T. D. Turner, J. L. Browning, and M. A. Widmayer, *Neuropeptides*, **32**, No. 2, 141-149 (1998).