Effects of β-Endorphin on Cardiac Afferent Systems

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Studies performed on cats have shown that the antifibrillatory effect of β-endorphin under acute myocardial ischemia is mediated by afferent pathways of the vagus nerves and sympathetic components of arrhythmogenesis. This effect is associated with the ability of β-endorphin to change the impulse activity of cardiovascular and integrative neurons of the nodose ganglion.

Key Words: *β-endorphin, vagus nerves, nodose ganglion, myocardial ischemia, cardiac adrenergic reactivity*

Clinical and experimental data point to a relationship between the severity of ischemic heart disease and the decrease in the plasma level of β-endorphin (BE). A moderate increase in the BE content is generally associated with good prognosis in patients with myocardial ischemia [1,2,5]. Our previous studies revealed a protective effect of BE in respect of the development of ischemic ventricular fibrillation. Bilateral vagotomy abolished this effect [9]. Vagotomy interrupts the conduction of impulses over afferent and efferent pathways of the vagus nerves (VN). Therefore, it is unclear what a pathway mediates the antifibrillatory effects of BE. Cardiac afferent systems play an important role in the pathogenesis of ischemic ventricular fibrillation. This work was designed to determine the role of vagal afferents in the antiarrhythmic effect of BE.

MATERIALS AND METHODS

Experiments (n=82) were performed on male and female cats weighing 2-4 kg narcotized with Nembutal (40 mg/kg intraperitoneally). Myocardial ischemia was induced by ligation of the left circumflex coronary artery at the site of its origin from the main branch. The development of arrhythmia was observed during 15-min arterial occlusion and 15-min reperfusion. Under these conditions idioventricular rhythm, ventricular tachycardia, and ventricular fibrillation were observed in 72%, 28%, and 55% of animals, respectively [7]. Electrocardiogram and blood pressure in the femoral artery were recorded with a BIOKOMB-8 polyphysiograph (ORION/EMG). Single and multiple extrasystoles, ventricular tachycardia, and ventricular fibrillation were considered in the analysis of arrhythmia.

In the first series of experiments, 8 cats were subjected to coronary artery occlusion accompanied by the injection of BE under differentiated blockade of the impulse conduction along myelinated VN fibers induced by cooling VN to 6°C [11]. Cervical VNs were separated from the sympathetic nerves and placed on a special nerve-cooling device equipped with a thermistor registering the nerve temperature. These nerves were thoroughly isolated from surrounding tissues. The nerve temperature was lowered using a cooling liquid which was pumped with a vacuum device 5 min before coronary artery occlusion and during ischemia and 15-min reperfusion. In the second series of experiment, 10 cats were subjected to similar procedures without administering BE. In the third series of experiments (24 animals), the pulse activity of the nodose ganglion neurons was extracellularly registered with a M-42 myograph (MEDICOR) using glass electrodes filled with 2.5 M KCl. The animals were injected with BE. In each series of experiments, neuronal

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activity was determined, ECG was monitored (II standard lead), and arterial pressure (AP) and pneumogram were measured using an EMT-35 electromanometer (Elema-Schonander). All results were recorded with an SDR-41 magnetograph (Nihon Kohden). In the fourth series of experiments (24 animals), the impulse activity of the nodose ganglion neurons was recorded after administration of Ringer's solution. In the fifth series of experiments (16 animals), the heart sensitivity to norepinephrine was determined. We analyzed changes in AP in the left ventricle, the dynamics of chronotropic effects, an integrative index of cardiac activity [10] in response to a standard dose of norepinephrine (1 μg/kg). Norepinephrine was injected into the right ventricle before a dropwise infusion and on the 5th and 15th minutes of the infusion of BE or Ringer's solution. Cardiac reactions were analyzed 20 sec (the maximum cardiac response phase) and 180 sec (the cardiac response decay phase) after the administration of norepinephrine [4]. BE was obtained from the Laboratory of Peptide Synthesis of the Cardiology Research-and-Production Center. BE was administered in a dose of 50 μg/kg either intravenously (the first and the fourth series) or into the right auricle (1 ml; the third series). Results were statistically analyzed by the Student's t, χ^2, and sign tests.

RESULTS

In the first series of experiments idioventricular rhythm, multiple extrasystoles, ventricular tachycardia, and ventricular fibrillation were observed in 75%, 50%, 50%, and 62.5% of animals, respectively. Similar results were obtained in the second series of experiments on the ischemic myocardium under blockade of the impulse conduction over myelinated VN fibers without BE administration (80%, 60%, 50%,

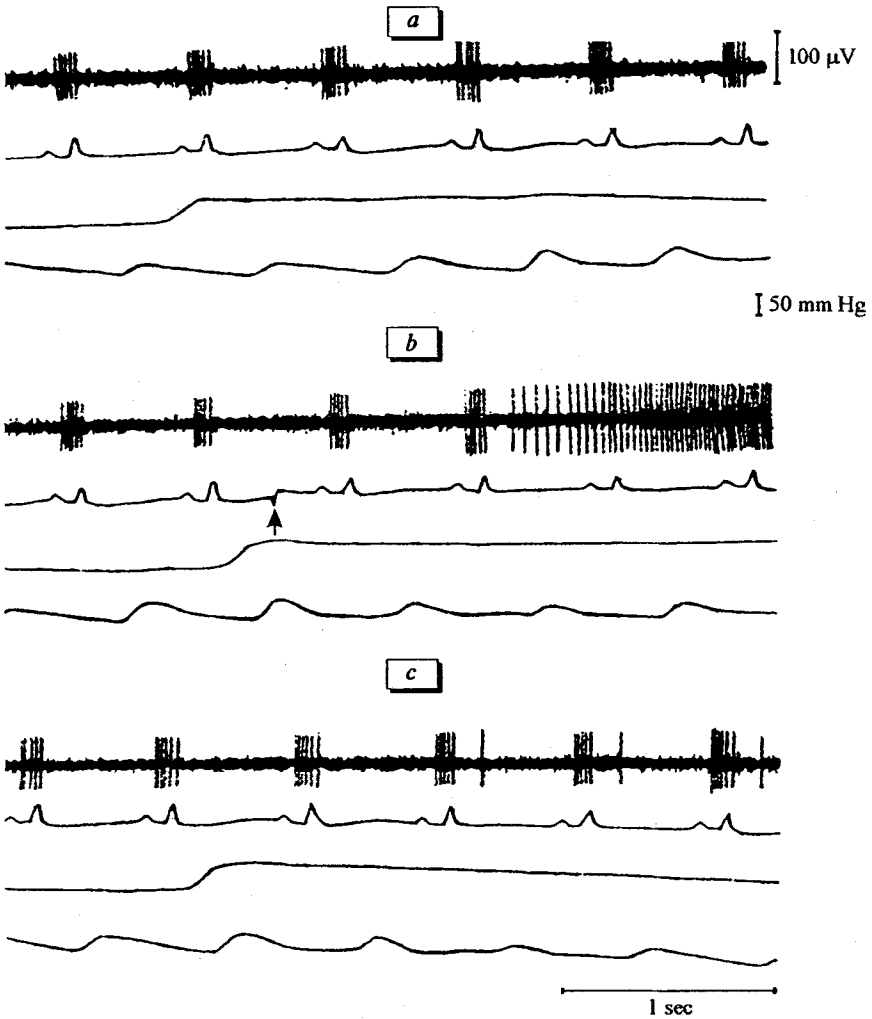

Fig. 1. Reaction of a pulse-synchronous cardiovascular neuron to β-endorphin: *a*) background activity; *b*) administration of β-endorphin (arrow); and *c*) 15 min after the injection. Here and in Figs. 2 and 3 (from top to bottom): neurogram, electrocardiogram (the isoline shift corresponds to the injection), pneumogram, and arterial pressure in the left femoral artery.

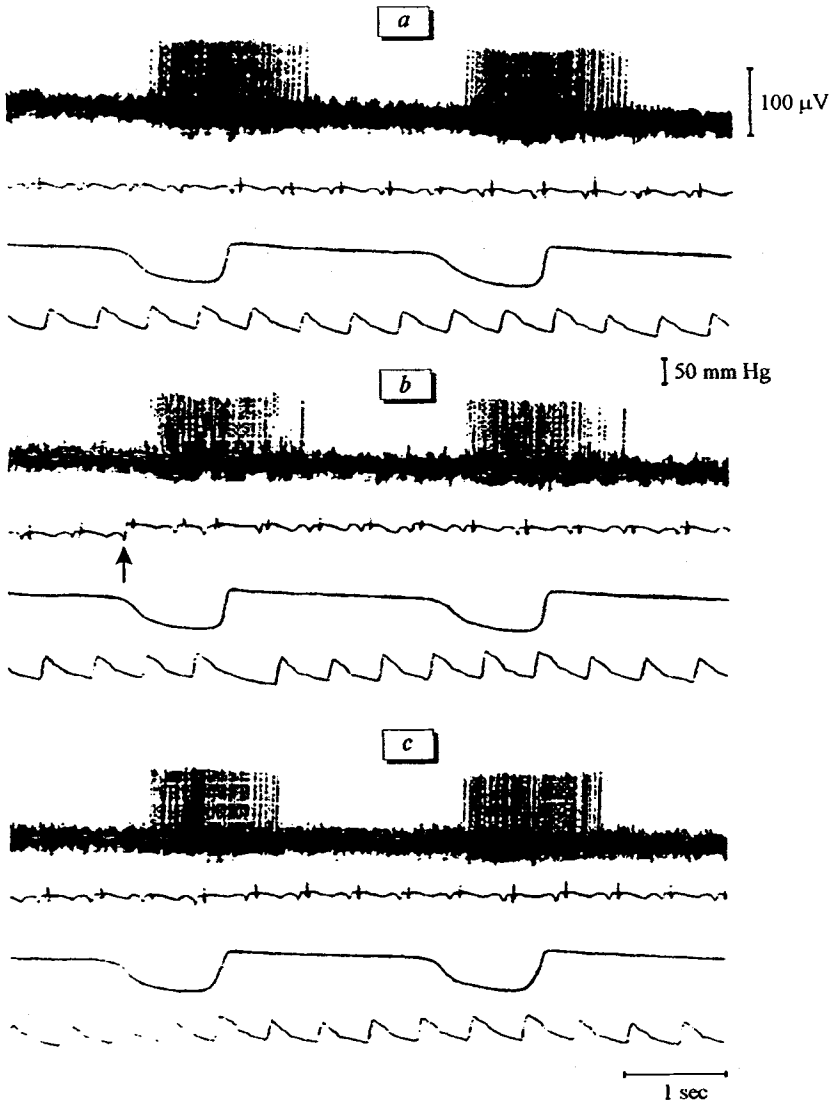

Fig. 2. Reaction of an inspiratory-expiratory neuron to the injection of β-endorphin: *a*) background activity; *b*) injection of β-endorphin (arrow); and *c*) 3 min after the injection.

and 40%, respectively). Thus, the blockade of myelinated VN fibers inhibited protective effects of BE. This indicates that antiarrhythmic effects of BE are determined by afferent impulses conducted into the central nervous system along myelinated VN fibers.

The information which is conducted to the bulbar cardiovascular center from cardiovascular and integrative neurons of the nodose ganglion plays an important role in the genesis of ischemic arrhythmia [3,6,8]. Therefore, in the third series of experiments we studied the influence of BE on the impulse activity of neurons belonging to these groups. The first group consisted of 8 neurons receiving information from the cardiovascular system (pulse-synchronous and irregular neurons). The second group consisted of 22 integrative neurons (cardiopulmonary, late inspiratory, and inspiratory-expiratory neurons and constant neurons with respiratory modulation).

The impulse activity of 87.5% of cardiovascular neurons increased (starting from the first or the second cardiac cycle) after the injection of BE (Fig. 1). The number of neurons with altered impulse activity decreased by two times to the 3 min after BE administration. Only 33% of neurons with altered impulse displayed activity on the 15th min. The impulse activity of other neurons returned to the control levels.

Integrative neurons receiving information from the cardiovascular and the respiratory systems responded to BE starting from the first or the second cardiac cycle in 22.7% of experiments. The impulse activity increased in 13.6% of these neurons. The impulse activity of 9.1% neurons decreased. The

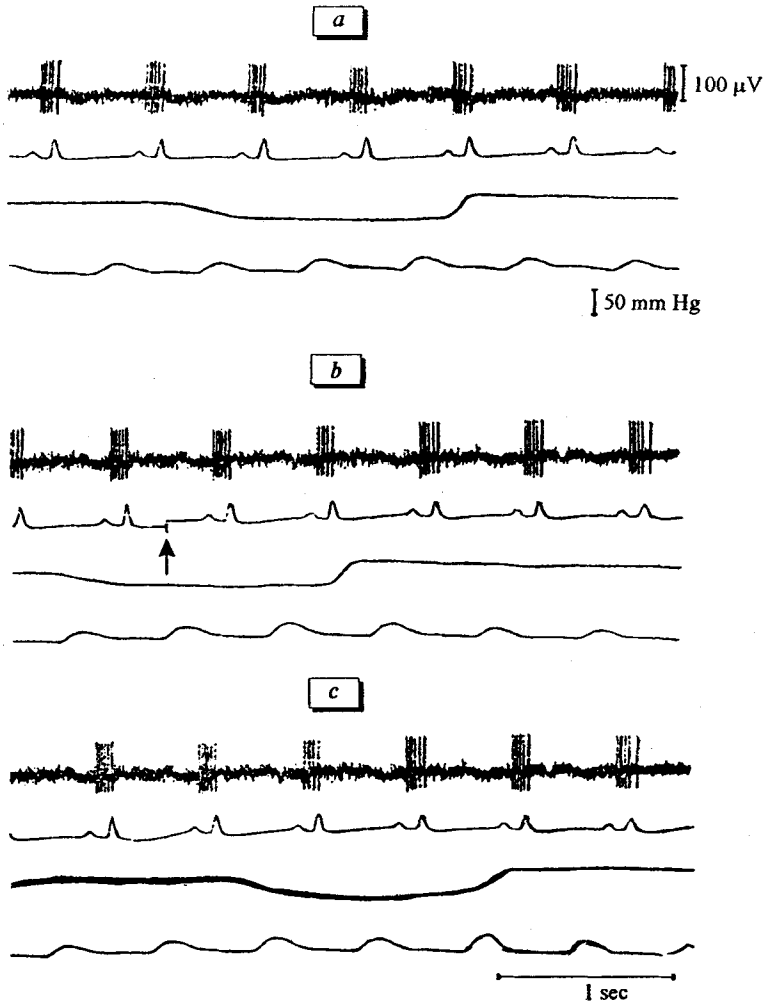

Fig. 3. The absence of the reaction of a pulse-synchronous cardiovascular neuron to Ringer's solution: *a*) background activity; *b*) injection of Ringer's solution (arrow); and *c*) 15 min after the injection.

number of integrative neurons responding to BE increased to 55% on the 3rd min after the injection and retained at this level untie the 15th min of observations (Fig. 2).

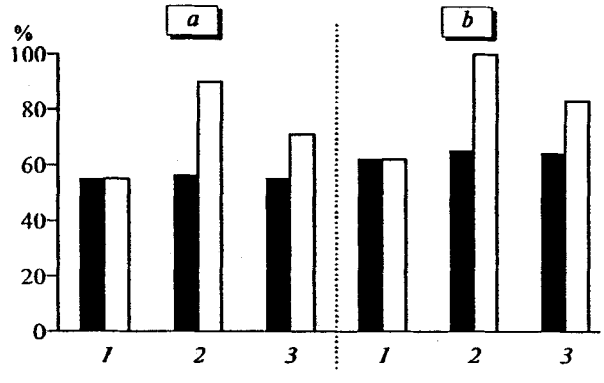

Fig. 4. Norepinephrine-induced changes in *a*) the left auricle pressure and *b*) the Opie index under infusion of Ringer's solution (dark bars) or β-endorphin (light bars): *1*) before infusion and the 5th (*2*) and the 15th min (*3*) of infusion.

In all series of experiments, BE increased AP. On the 3rd min after administration of BE, AP was high in 20% of experiments; it decreased and was lower than initial level in 47% of experiments. In the majority of animals, on the 15th min AP was lower than the initial level. BE did not change the heart rate. A transient and moderate decrease in the heart rate was observed in 6% of experiments.

The hemodynamic reaction began 4 sec (3.9± 0.6 sec) after BE injection. However, the latency of changes in the impulse activity of cardiovascular neurons was 0.48±0.08 sec after the injection of BE. This indicates that the reaction of cardiovascular neurons revealed in our experiments was not due to changes in AP. Changes in the activity of the majority of integrative neurons were observed when AP had shifted.

The main objective in the control series of experiments was to exclude a possible involvement of changes in the right auricle volume in the reaction

of cardiovascular neurons to BE. Changes in neuronal impulse activity after an intra-auricular administration of Ringer's solution in a volume equal to that of BE were not observed (Fig. 3). Therefore, the reaction of the nodose ganglion neurons occurring within the first seconds after administration of BE was caused by BE, but not by changes in the right auricle volume.

The AP elevation observed during the first seconds after the injection of BE was probably associated with the ability of this substance to increase blood catecholamine content [12]. The decrease in AP on the 3rd min after administration of BE was probably due to attenuation of sympathetic effects on the heart resulting from a BE-induced increase in cardiac afferent impulses.

To confirm this suggestion, we studied the effects of BE on adrenergic reactivity of the heart by analyzing cardiac reactions to a standard dose of norepinephrine administered simultaneously with BE and Ringer's solution (the fifth series of experiments). Myocardial adrenergic reactivity did not change in animals injected with Ringer's solution. However, the cardiac response to norepinephrine was more pronounced in animals injected with BE (in 87% of experiments) ($p<0.05$, Fig. 4). The increased cardiac response was probably due to a BE-induced decrease in the secretion of endogenous norepinephrine from sympathetic cardiac terminals. This is confirmed by the fact that a decrease in the content of norepinephrine in the heart increases the number of functioning β-adrenoceptors [13].

Thus, the antifibrillatory effect of BE under acute myocardial ischemia is mediated by vagal afferent pathways. Obviously, BE-induced changes in the afferent outflow from cardiovascular and integrative neurons of the nodose ganglion affect the activity of the bulbar cardiovascular center. In myocardial ischemia, this is accompanied by the activation of compensatory reactions preventing the development of ventricular fibrillation. The decrease in sympathetic influence on the heart results from changes in neuronal impulse activity.

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