VAGOINHIBITORY ACTION OF ALPHA-ENDORPHIN

G. E. Samonina and E. P. Karazeeva

UDC 615.31:[547.943:547.95].015.4:612.819.91].07

KEY WORDS: alpha-endorphin; parasympathetic bradycardia

Various neuropeptides, including opioid peptides, have been discovered in quite high concentrations in the medium and endings of sympathetic and parasympathetic fibers [13, 14]. During activation of the sympathetic or parasympathetic nervous system, besides the classical mediators, neuropeptides also are released. There is evidence [11] that opioid peptides are involved in sympathetic-parasympathetic interaction, including in regulation of the cardiac rhythm. The possibility cannot be ruled out that during excitation of sympathetic nerves, neuropeptides released in the heart may inhibit vagal bradycardia. This hypothesis is perfectly sound, because an inhibitory effect of neuropeptides, including opioid peptides, has been described on vagal bradycardia [12, 15]. Alpha-endorphin is synthesized in quite considerable amounts in the human and animal body, and its level in human blood plasma may reach almost 1 ng/ml [5-7]. There is evidence that alpha-endorphin induces various changes in function of the physiological systems of the body, such as a rise of blood pressure and a reduction of the heart rate [3].

The aim of this investigation was to study the effect of alpha-endorphin on parasympathetic bradycardia.

EXPERIMENTAL METHOD

Experiments were carried out on frogs. The ECG and cardiointervalogram were recorded, the amplitude of the latter reflecting the duration of the cardiac cycle. Parasympathetic bradycardia was induced by short-term stimulation of the peripheral end of the divided vagosympathetic trunk (1-5 V, 10-20 Hz, 0.1 msec, duration of stimulation 100-300 msec). The magnitude of the effect was calculated as the ratio, in per cent, between the most altered duration of the cardiac cycle and its initial duration. After relatively stable effects had been obtained (±10%), 0.1 ml of a solution of alphaendorphin in a concentration of between $1 \cdot 10^{-8}$ and $1 \cdot 10^{-4}$ g/ml was injected intravenously, and every 3 min later stimulation was repeated with the same parameters for 30-60 min. To reveal the significance of the difference between the original values of bradycardia and bradycardia superposed on alphaendorphin, the Wilcoxon—Mann—Whitney nonparametric test [4] was used. The confidence interval was calculated by a rapid method, with a 95% level of significance [2].

EXPERIMENTAL RESULTS

Stimulation of the peripheral end of the vagosympathetic trunk caused slowing of the heart, by a degree which varied in different experiments from 6 to 75% of the original heart rate. Bradycardia appeared after a short latent period, and it was abolished by intravenous injection of atropine sulfate (0.1 mg/100 g). In some experiments slowing of the heart rate was followed after a long latent period by sympathetic quickening of the cardiac rhythm, which in turn was abolished by the beta-adrenoblocker propranolol (0.2 mg/100 g, intravenously). We studied only the first effect, namely parasympathetic bradycardia.

Intravenous injection of alpha-endorphin (0.1 ml), in none of the concentrations tested, was accompanied by changes in the original heart rate. Low concentrations of alpha-endorphin ($1 \cdot 10^{-8} \cdot 10^{-6}$ g/ml) were not accompanied by any change in vagal bradycardia. Injection of alpha-endorphin in high concentrations reduced the parasympathetic slowing of the heart, and the depth of inhibition of the effect increased with an increase of concentration. A concentration of $1 \cdot 10^{-5}$ g/ml reduced vagal

Department of Human and Animal Physiology, Moscow University. (Presented by Academician of the Academy of Medical Sciences of the USSR I. P. Ashmarin.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 111, No. 2, pp. 174-175, February, 1991. Original article submitted April 6, 1990.

0007-4888/91/0002-0207$12.50

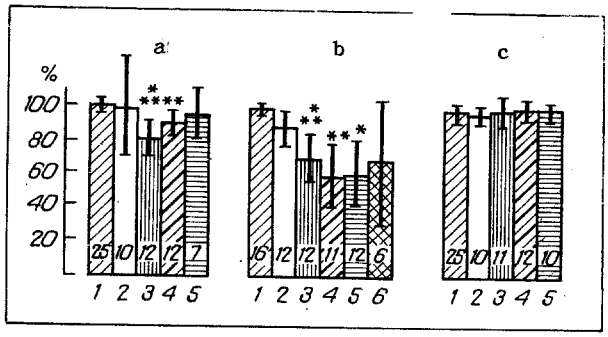

Fig. 1. Diminution of parasympathetic slowing of heart rate, associated with action of various concentrations of alpha-endorphin. a) 0.1 ml of alpha-endorphin, $1 \cdot 10^{-5}$ g/ml; b) 0.1 ml of alpha-endorphin, $1 \cdot 10^{-4}$ g/ml; c) 0.1 ml physiological saline. Numbers in columns denote number of experiments. 1) Initial value; 2-6) at the following times after injection of alpha-endorphin: 2) 1-3 min, 3) 4-8 min, 4) 9-15 min, 5) 16-30 min, 6) 31-60 min. Vertical axis — magnitude of effect (in per cent of initial value). *$p < 0.01$, **$p < 0.005$, ***$p < 0.001$.

bradycardia by only 20% (Fig. 1a), whereas a high concentration ($1 \cdot 10^{-4}$ g/ml) inhibited bradycardia by 40% (Fig. 1b). Control injection of 0.1 ml of Ringer's solution, like injection of alpha-endorphin in low concentrations, was not accompanied by any change in parasympathetic slowing of the heart (Fig. 1c).

Inhibition of vagal bradycardia, incidentally, did not take place immediately after injection, but it developed slowly. It will be clear from Fig. 1 that the greatest decrease in magnitude of the bradycardic effect with a concentration of $1 \cdot 10^{-5}$ g/ml was observed 4-8 min after injection of the peptide, whereas with a higher concentration, it could be delayed until the 9th-15th minutes. Later the original value of the effect was gradually restored. Thus alpha-endorphin, injected intravenously, causes inhibition of vagal bradycardia.

It is impossible at present to make any definite statement about the mechanisms of action of alpha-endorphin. It may act on the presynaptic level, blocking acetylcholine release from parasympathetic postganglionic endings in the heart. The possibility likewise cannot be ruled out that its influence is realized at the postsynaptic level also.

We showed previously that sydnophen, a psychostimulant of the phenylalkylsydnoneimine series [1], besides its central psychostimulant activity, also possesses peripheral vagolytic properties [8-10]. These vagolytic properties are manifested as inhibition or even complete abolition of parasympathetic bradycardia arising in response to stimulation of the peripheral end of the divided vagus nerve. Several possible mechanisms of this property of sydnophen can be suggested, one of which is the release by sydnophen of neuropeptides which, in turn, inhibit the vagal effect.

Comparison of the inhibitory action of alpha-endorphin and sydnophen on vagal bradycardia must take account of the fact that sydnophen also caused a maximal decrease of vagal bradycardia in frogs after a delay of 16-20 min [10]. If it is recalled that the maximal inhibition of parasympathetic slowing of the heart against the background of alpha-endorphin takes place after 4-8, or even 9-15 min, the relative times of action of sydnophen and alpha-endorphin can be seen to be an argument in support of our hypothesis relative to the possible role of neuropeptides in the vagolytic properties of sydnophen.

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