TABLE 2. Accumulation of LPO Products and [^{3}H]Serotonin Release under the Influence of Different Procedures (M ± m)

Type of procedure	MDA, nmoles/mg protein	Fluorescent products, % of control	Change in release, % of control
Control	4,93±0,45	100±15	0
Stimulation of LPO (0.5 mM ascorbate + 10 μM Fe^{++})	18,2±0,56	—	95±3
Stimulation of release (KCl)	4,57±0,49	95±15	43,3±5
Inhibition of LPO (4-methyl-2,6-di-tert-butylphenol)	4,90±0,45	93±12	33±3

Legend. Duration of exposure 10 min.

Meanwhile the antioxidant stimulates mediator release and at the same time completely blocks LPO in the synaptosomal membranes. In other words, the action of LPO activators and of the antioxidant on mediator uptake and release is similar in direction.

The results in Table 2 are thus evidence of absence of correlation between changes in the content of phospholipid peroxidation products in synaptosomal membranes and the efficiency of serotonin release, and taken as a whole they suggest that the effects of antioxidants thus revealed are not mediated through mechanisms of inhibition of phospholipid peroxidation.

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ROLE OF THE OPIOIDERGIC SYSTEM IN RESPIRATION CONTROL

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UDC 616.24-008.4-02:615.212.7:547.943/-092.9

KEY WORDS: morphine; enkephalin analog; respiration; electromyogram; TSH releasing factor; naloxone; bradykinin; opiate receptors.

One of us (V. M. B. [1]) showed in experiments on rats that certain peptides (bradykinin, TSH releasing factor, $ACTH_{4-7}$ fragment, melanostatin analog), when injected intravenously, weaken the analgesic effect of morphine and of enkephalin analog Tyr-D-Ala-Gly-Phe(NO_2)NH_2, which is equal to morphine in its analgesic activity. Fragment $ACTH_{4-7}$ and melanostatin analog have no marked effect on respiration parameters in waking rabbits and do not abolish respiratory depression due to morphine and enkephalin analog in animals. TSH releasing factor (TSHRF) completely abolishes respiratory depression caused by morphine and enkephalin analogs in doses not changing morphine analgesia [1].

The object of this investigation was to compare the effect of the opiate antagonist naloxone and of TSHRF and bradykinin on respiratory depression caused by morphine and enkephalin analog Tyr-D-Ala-Gly-Phe(NO_2)NH_2.

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(Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 96, No. 10, pp. 57-59, October, 1983. Original article submitted March 25, 1983.

0007-4888/83/9610-1408$07.50

EXPERIMENTAL METHOD

Experiments were carried out on 42 rats weighing 180-200 g, anesthetized with urethane (0.8 g/kg). By means of implanted bipolar silver electrodes the electromyogram (EMG) of the diaphragm was recorded in the animals in crude and integrated form [2]. Respiratory volume was calculated from the amplitude of the EMG and the respiratory minute volume was estimated as the product of the mean amplitude of the EMG volleys and their frequency. The state of the animals was monitored by recording the ECG in one standard lead and the blood pressure through a cannula introduced into the common carotid artery. All parameters were recorded on an SDR-41 magnetic recorder (Nihon Kohden, Japan), and they were monitored visually at the same time on the screen of a Disa 51200 oscilloscope. In the course of the experiment the EMG of the diaphragm was under constant visual and acoustic control by means of the Disa oscilloscope and AR-1 unit of the magnetic recorder. To analyze the data, individual segments of the magnetic record, after examination on the oscilloscope, were recorded on paper tape by means of a PF-14b polygraph (Biomedica, Italy). Enkephalin analog Tyr-D-Ala-Gly-Phe(NO_2)NH_2, TSHRF, and bradykinin were obtained in the Laboratory of Peptide Synthesis, All-Union Cardiologic Scientific Center, under the direction of Dr. Chem. Sci. M. I. Titov. All substances for testing were injected intravenously.

EXPERIMENTAL RESULTS

Immediately after injection of morphine and enkephalin analog in a dose of 0.20-0.25 mg/kg respiration became slow and deep and in some experiments this was preceded by a short period (a few seconds) of apnea. The amplitude of the respiratory volleys of the EMG then gradually diminished but the respiration rate increased, but in the experiments with morphine it remained below its initial value and in the experiments with enkephalin analog it was a little higher than initially. At the 4th minute after injection the respiratory minute volume fell in the experiments with morphine on average by 48% and in the experiments with enkephalin analog by 56% compared with the initial level. During inhibition of respiration by morphine a disturbance of the regular rhythm of respiratory volleys of the EMG was sometimes observed, but this was not found in the experiments with enkephalin analog. The original level of the respiratory minute volume was restored 12-15 min after injection of the analgesics.

The depressant action of morphine and enkephalin analog on the respiratory center, estimated from the time course and duration of inhibition of respiration, was thus about equal. However, unlike morphine the enkephalin analog did not reduce, but actually increased the respiration rate a little and did not disturb the rhythm of respiration.

In control experiments naloxone in doses of 0.25-0.30 mg/kg caused excitation of the respiratory center, characterized by an increase in frequency and amplitude of the respiratory volleys of the EMG. Bradykinin and TSHRF, injected in the same doses, also stimulated respiration, but unlike naloxone, bradykinin increased mainly the amplitude, whereas TSHRF increased mainly the frequency of the respiratory volleys. Unlike naloxone and bradykinin, TSHRF caused tonic activity of the diaphragm in between volleys. It must also be pointed out that TSHRF caused practically no change in the mean blood pressure unlike naloxone and, in particular, bradykinin, which induced a depressor vascular response that varied in degree and duration.

Naloxone, bradykinin, and TSHRF, injected in doses of 0.25-0.30 mg/kg, had a stimulating action on the respiratory center at the 4th minute after injection of morphine or enkephalin analog (Fig. 1). However, the intensity of this excitatory effect differed in experiments with the different analgesics. In the experiments with morphine the respiratory minute volume not only reached its initial level after injection of the test antagonists (before injection of the analgesic), but exceeded it by 40-60%. Meanwhile, in the experiments with enkephalin analog the respiratory minute volume only reached its initial level by this time or, in some experiments, exceeded it by not more than 10-15%.

The results confirm observations of some workers on the participation of opiate receptors in the function of external respiration [3, 4]. This hypothesis is supported by the inhibitor action of morphine and enkephalin analog which the present writers observed on respiration and the stimulating effect of the antagonist studied in these experiments on respiration. The time course of inhibition of respiration by morphine and by enkephalin analog was similar, but differences in the action of these analgesics on the frequency and rhythm

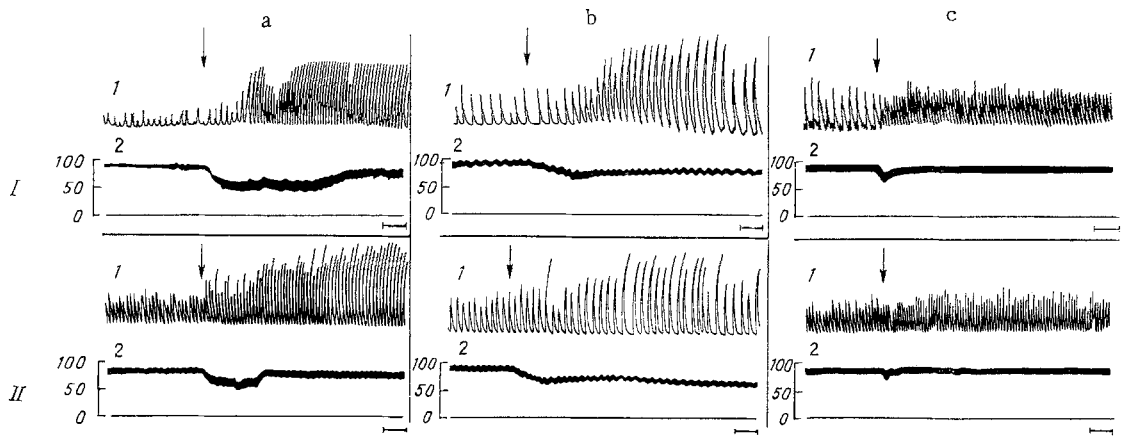

Fig. 1. Effect of naloxone (a), bradykinin (b), and TSHRF (c) on respiratory depression induced by morphine (I) and enkephalin analog (II). 1) Integrated EMG of diaphragm, 2) arterial pressure (in mm Hg). Arrow indicates time of injection of substance. Time marker 4 sec.

of respiration suggest that opioidergic reception in the respiratory system is heterogeneous. This situation can evidently explain differences in the action of naloxone, bradykinin, and TSHRF on respiration in the initial state and when inhibited by analgesics. The marked ability of bradykinin to increase mainly the depth, but of TSHRF to increase mainly the frequency of respiration suggests that their naloxone-like effect is mediated through different populations of opiate receptors participating in the regulation of breathing.

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USE OF THE ANTIOXIDANT IONOL TO PREVENT DAMAGE TO THE HEART CAUSED BY PROLONGED ANTITUBERCULOSIS MEDICATION

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UDC 615.281:579.873.21/.065:616.12/.015.25:615.243.4

KEY WORDS: isoniazid; prothionamide; rifampicin; heart; antioxidant ionol.

It was shown previously that prolonged administration of antibacterial antituberculosis preparations (ABP) to intact animals has a cardiotoxic action, manifested by marked destructive and dystrophic changes in the heart muscle [7]. A comparative study of different combinations of ABP showed that a combination of ABP such as isoniazid, prothionamide, and rifampicin may have a marked toxic action on the cardiovascular system [7].

The investigation described below had two aims: first, to detect and evaluate quantitatively functional and metabolic disturbances of the myocardium arising during prolonged administration of ABP, and second, to attempt to prevent these disturbances by means of the synthetic antioxidant ionol [1].

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Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 96, No. 10, pp. 59-62, October, 1983. Original article submitted December 31, 1982.

 0007-4888/83/9610-1410$07.50