EFFECT OF NALOXONE AND THYROTROPIN RELEASING HORMONE ON RESPIRATION IN ACUTE HYPOXIA

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KEY WORDS: thyrotropin releasing hormone; respiration; dyspnea; apnea; acute hypoxia; blood loss.

There is now conclusive proof that function of the respiratory center is influenced by the opioidergic system [9, 10, 13]. In particular, it has been shown that the depressant action of morphine and certain endogenous opioids (endorphins and enkephalins) on respiration can be abolished by naloxone, a specific antagonist of narcotic analgesics [1, 2, 8, 14, 15]. There have also been isolated reports that naloxone can stimulate respiration during asphyxia [7, 12].

The aim of this investigation was to study the effect of naloxone and of thyrotropin releasing hormone (TRH), which gives rise to several antiopiate effects, on respiration under conditions of acute hypoxia.

EXPERIMENTAL METHOD

Experiments were carried out on 48 rats weighing 180-200 g, anesthesized with urethane (0.8 g/kg). Hypoxia was induced by bleeding for 2-3 min through a catheter introduced into the central end of the divided common carotid artery. Blood loss amounted to about 30% of the total blood volume. To prevent the blood from clotting, the rats were given heparin. Respiratory function was estimated from the crude and averaged electromyograms (EMG) of the diaphragm [3, 5]. To monitor the animals' state, the blood pressure (BP) in the common carotid artery and the ECG in one standard lead were recorded. In the course of the experiment the parameters were recorded continuously on an SDR-41 magnetic recorder (Nihon Kohden, Japan), after which individual cuts of this record were transferred to paper tape of a PF 14B polygraph (Biomedica, Italy) for analysis. In addition, in the course of the experiment the crude EMG of the diaphragm also was monitored with acoustic control. The substances to be tested, namely naloxone hydrochloride (from Winthrop, USA) and TRH (obtained in the Laboratory of Peptide Synthesis, All-Union Cardiologic Scientific Center, under the direction of Dr. Chem. Sci. M. I. Titov), were injected as a single dose of 0.25-0.30 mg/kg through a catheter into the jugular vein.

EXPERIMENTAL RESULTS

In control experiments (seven animals) changes in respiration during the development of hypoxia induced by acute blood loss were of the typical character frequently described in the literature [3, 4]: Initially the rate and depth of respiration were increased, with the appearance of occasional infrequent deep inspirations, followed by a decrease in the frequency and amplitude of respiration and disturbance of its rhythm (dyspnea), after which preterminal respiratory arrest (preterminal apnea) developed. The time when bleeding stopped, when the assigned volume of blood had been removed, usually coincided with the dyspneic stage of disturbance of respiration or with the onset of preterminal apnea. The mean BP at the time when bleeding ceased had fallen from 95 ± 14 to 16 ± 4 mm Hg and it remained at a low level until death of the animals. Breathing was restored after apnea, in various terminal forms: In some experiments breathing became infrequent but deep, of gasping type, whereas in others it became infrequent and superficial. Sometimes periodic breathing of Biot

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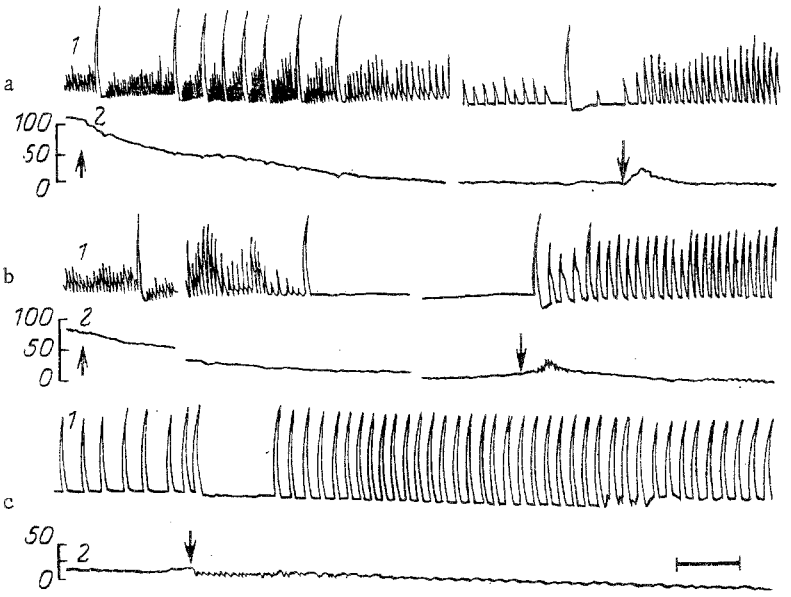

Fig. 1. Effect of naloxone and TRH on respiration and BP in rats after acute blood loss. a, b) Injection of naloxone; c) injection of TRH. 1) Averaged EMG of diaphragm, 2) BP in common carotid artery (in mm Hg). Arrow pointing upward indicates beginning of bleeding, arrow pointing downward indicates injection of naloxone (a, b) and TRH (c). Time marker 10 sec.

type appeared. The animals in the control experiments died because of respiratory arrest and progressive disturbances of cardiovascular functions.

Naloxone and TRH were injected into the animals in the posthemorrhagic period at different stages of disturbances of respiratory function: dyspnea, preterminal apnea, and agonal forms of respiration.

In the stage of dyspnea, naloxone (eight experiments) increased the frequency and depth of respiration. The mean duration of the response was 1 min, after which a gradual decrease in the frequency of respiration and amplitude of the EMG of the diaphragm was observed (Fig. 1a). Injection of naloxone in the period of preterminal apnea (six experiments) caused rapid recovery of regular breathing (Fig. 1b). Against the background of terminal respiration of gasping type naloxone caused temporary respiratory arrest, followed by some quickening of breathing and changes in amplitude of the EMG of the diaphragm in either direction (five experiments).

TRH, like naloxone, stimulated respiration in the posthemorrhagic period at different stages of disturbance of respiratory function. However, unlike naloxone, TRH caused the appearance of weak, continuous impulsation between bursts on the EMG of the diaphragm at the dyspnea stage in all six experiments. Similar activity, sometimes arising also in the period of apnea in response to injection of TRH (five experiments), later changed into regular bursts of activity. Changes in terminal respiration of gasping type under the influence of TRH (six experiments) were of the same character as in response to injection of naloxone (Fig. 1c). Naloxone and TRH in the posthemorrhagic period as a rule evoked an increase in BP that differed in degree and duration. However, the stimulating effect of opioid antagonists on respiration in this period did not correlate with the degree of rise of BP. At the same time the possibility cannot be ruled out that the activating action of antagonists on respiration may be due, at least partly, to possible improvement of the cerebral circulation on account of the redistribution of the blood flow in the body.

Data in the literature suggest the presence of opiate receptors, pulmonary [16] and central, located on neurons of the respiratory center [6, 13-15], through which the stimulating action of opioid antagonists on respiration may be realized. To test this hypothesis an additional series of experiments was carried out on five rats, in which the vagosympathetic trunks were divided bilaterally before blood loss. In these animals the stimulating action of naloxone and TRH on respiration was found to be preserved in the posthemorrhagic period.

This fact suggests that pulmonary receptors do not play an essential role in the stimulating action of naloxone and TRH on breathing.

The results of this investigation do not contradict the limited information present in the literature on the stimulating effect of opioid antagonists on respiration during hypoxia. Disturbances of respiration arising during the development of acute hypoxia due to blood loss are evidently due to a definite extent to the action of endogenous opioid peptides, whose inhibitory effect on respiratory center neurons is abolished by naloxone and TRH. This hypothesis does not rule out other possible mechanisms of the stimulating action of opioid antagonists on respiration in actute hypoxia.

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TWO FUNCTIONS OF PROTEOGLYCANS IN ERYTHROCYTE AGGREGATION AND ADHESION

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The writers' previous investigations showed that normal potassium salts of hyaluronic acid (HUA), of soluble protein-chondroitin-keratan sulfate (PCKS), and proteoglycan aggregates (PA) of cartilage, which are highly important components of different kinds of cells and the matrix of connective tissue, besides their many other funtions, also play the role of factors preventing dispersion of cells and other tissue elements, displacing them from the space occupied by proteoglycans, and concentrating them in a limited volume. Thus these biopolymers promote aggregation and subsequent and nonspecific adhesion of cells and also the formation of certain extracellular tissue structures [5-8]. Investigations of the aggregating action of proteoglycans on cells of the retina and other tissues, by a number of workers, have completely confirmed the above theory [6]. It has, moreover, been suggested that the ability of proteoglycans to displace cells nonspecifically into the smallest possible space is of essential important for morphogenesis also [12]. Howsever, the nonspecific and reversible stereochemical action of HUA, PCKS, and PA on cell aggregation does not rule out

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