COMBINED ACTION OF HYPOXIA AND HYPERCAPNIA ON FUNCTIONAL STATE OF THE RESPIRATORY CENTER

A. M. Kulik and L. N. Kondrat'eva

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Discharges of bulbar respiratory neurons and electrical activity of the diaphragm and intercostal muscles were studied and pO_2, pCO_2, pH, and the oxygen saturation of the arterial blood were determined in cats anesthetized with pentobarbital and exposed to the combined action of hypoxia and hypercapnia. During inhalation of a hypoxic gas mixture the developing hypocapnia disturbed the firing pattern of the respiratory neurons and respiration of the Cheyne–Stokes type was established. Addition of 2% CO_2 to the hypoxic gas mixture restored the arterial blood gas composition to its initial level, prevented the development of hypocapnia, and prevented the disturbance of the rhythmic firing pattern of the respiratory neurons. Addition of 5% CO_2 to the hypoxic gas mixture had a negative action: respiratory unit activity was first stimulated, then inhibited, metabolic and respiratory acidosis was induced, and asphyxia developed.

KEY WORDS: respiration; hypoxia; hypercapnia; respiratory neurons.

Experimental investigations have shown that the addition of CO_2 to a hypoxic gas mixture increases the resistance of the body to hypoxia as a result of the action of CO_2 on all systems supplying the organs and tissues with oxygen [2, 3, 5, 8, 10, 13-17, 19]. The use of thermoelectric and polarographic methods showed that the addition of CO_2 to a hypoxic gas mixture acts primarily by producing a regional redistribution of blood in the body: the blood supply and oxygen partial pressure in the brain and heart tissues are improved whereas in the skeletal muscles they are sharply worsened [4, 11, 12].

The addition of CO_2 to the hypoxic gas mixture restores normal respiration and improves the functional state of the CNS [3, 5, 6, 8, 10, 13, 16, 18, 19]. However, the changes in unit activity, the coordination relations, and the functional properties of the bulbar respiratory neurons remained unstudied.

The object of this investigation was to study unit activity of the bulbar respiratory neurons and electrical activity of the respiratory muscles in conjunction with ventilation of the lungs and the composition of the blood gases in the course of hypoxia associated with normo-, hypo-, and hypercapnia.

EXPERIMENTAL METHOD

Experiments were carried out on 57 cats under pentobarbital (40 mg/kg body weight, intraperitoneally) anesthesia. Stereotaxic and microelectrode techniques were used. The tip of the metal microelectrode was 1-3 μ in diameter.

The animals inhaled gas mixtures of the following composition for 10 min: 10% O_2 in nitrogen, 10% O_2 + 2% CO_2; 10% O_2 + 5% CO_2. In the interval between the changes to inhalation of a new gas mixture, the animals breathed atmospheric air for 20-30 min.

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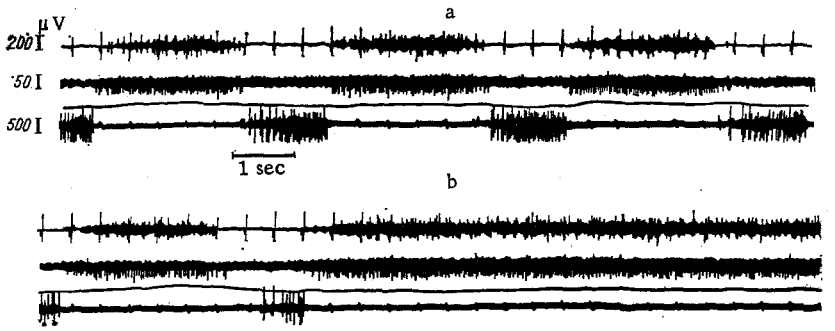

Fig. 1. Unit activity of bulbar inspiratory neurons and EMG of diaphragm and expiratory intercostal muscles of cat during inhalation of atmospheric air (a) and hypoxic gas mixture of 10% O_2 in nitrogen (b). From top to bottom: EMG of diaphragm, unit activity of respiratory neurons, pneumogram, EMG of expiratory intercostal muscles.

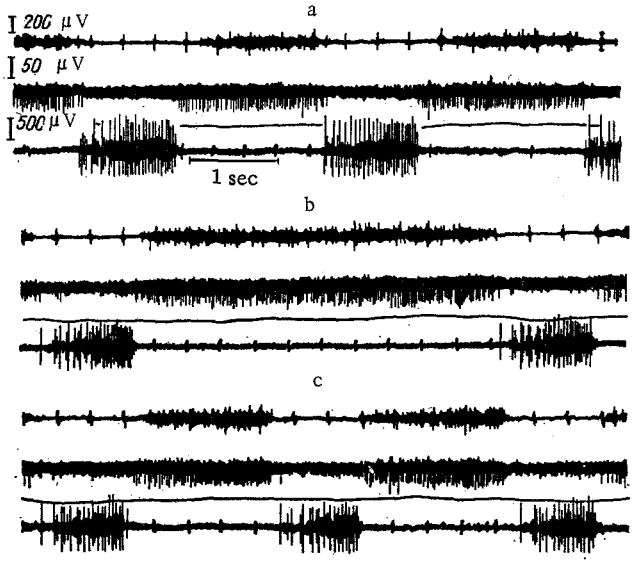

Fig. 2. Unit activity of bulbar inspiratory neurons and EMG of diaphragm and expiratory intercostal muscles of cat during inhalation of atmospheric air (a) and hypoxic gas mixture with 2% CO_2 (b, c). Legend as in Fig. 1.

Activity of bulbar respiratory neurons was recorded during inhalation of atmospheric air, inhalation of the gas mixture, and 10-20 min after stopping inhalation of the gas mixture. Parallel with respiratory unit activity the EMG of the diaphragm and intercostal muscles, the pneumogram, and the pulmonary ventilation were recorded.

The arterial-blood oxygen saturation was determined with a Brinkman's oxyhemometer, and pCO_2 and pO_2 of the blood by the method of Astrup and Siggaard-Andersen.

EXPERIMENTAL RESULTS AND DISCUSSION

During inhalation of the hypoxic gas mixture (10% O_2 in nitrogen) changes in the response of the respiratory neurons depended not only on the degree of hypoxic but also on the duration of exposure to it (Fig. 1). In the first 2-3 min the frequency and number of spikes of the inspiratory neurons were increased and activity of the expiratory neurons was reduced. The respiration rate was quickened and pulmonary ventilation was increased by 80% compared with initially. A specific rhythm of unit activity often appeared after 2-6 min: long volleys of the inspiratory neurons alternated with very short. The volleys of the expiratory neurons became less prolonged. Respiration acquired a pathological character of the Cheyne–Stokes type.

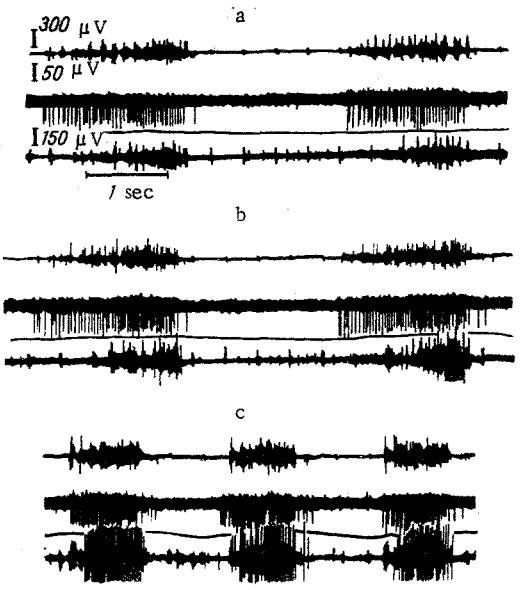

Fig. 3. Activity of bulbar inspiratory neurons and EMG of diaphragm and inspiratory intercostal muscles of a cat during inhalation of atmospheric air (a) and hypoxic gas mixture with 5% CO_2 (b, c). Legend as in Fig. 1.

The pulmonary ventilation was reduced and the respiration rate fell. The appearance of the specific rhythm of unit activity coincided with the development of acute hypocapnia. For the arterial blood at this time, pCO_2 was 22-18 mm Hg, pH was 7.48-7.52, and pO_2 was 55-50 mm Hg; in other words, a state of respiratory alkalosis was observed.

The change from a rhythmic to an aperiodic type of respiration during acute hypoxia thus took place as a result of disturbance of the rhythmic discharge pattern of the respiratory neurons at a time of sudden humoral changes in the arterial blood. After the inhalation of the hypoxic mixture had ceased and the animal had breathed ordinary air for 5-10 min, regular volleys of spikes were discharged by the respiratory neurons and the normal arterial blood gas composition was restored.

The animals were re-exposed to hypoxia after 20-30 min, the only difference being that 2% CO_2 was added to the hypoxic gas mixture. The response of the respiratory neurons to the combined action of hypoxia and hypercapnia had a marked biphasic character. In the first 1-2 min of inhalation of the combined gas mixture (Fig. 2b), long volleys of the inspiratory neurons with an increased firing rate was observed – the typical response to an excess of CO_2. After 2-5 min the character of the unit activity changed (Fig. 2c), the volleys of the inspiratory neurons were shortened, and there was a corresponding decrease in the number of spikes; a faster rhythm of respiratory unit activity was established and it persisted until the end of inhalation of the combined gas mixture. Characteristically, the activity of the expiratory neurons and expiratory muscles also was increased under these conditions, and not reduced as it was in hypoxia without CO_2 (Fig. 2). The consecutive reciprocal connection between the inspiratory and expiratory neurons and muscles was disturbed.

The level of the pulmonary ventilation remained high throughout the period of exposure to hypoxia with 2% CO_2 on account of an increase in the respiration rate; the pulmonary ventilation was increased by 100-120% over its initial level.

Throughout the period of inhalation of the hypoxic gas mixture with 2% CO_2, pCO_2 in the arterial blood fluctuated within its initial limits (29-32 mm Hg), the pH was restored to normal (7.32-7.36), the fall in pO_2 was slowed, and the oxygen saturation of the arterial blood was maintained at 78-80% (Fig. 2).

The addition of 2% CO_2 to the hypoxic gas mixture thus, first, restored the arterial blood gas composition to a level close to its initial values and prevented the development of hypocapnia, and second, prevented the disturbance of the rhythmic firing pattern of the respiratory neurons and the appearance of a pathological type of respiration.

To compare the action of different CO_2 concentrations under hypoxic conditions, in another series of experiments 5% CO_2 was added to the 10% O_2 in nitrogen (Fig. 3). During inhalation of a gas mixture of this composition, the biphasic response of the respiratory neurons was revealed more clearly still. During the first 2-3 min the inspiratory neurons continued to discharge in long volleys, and the number of spikes in the volley was increased (Fig. 3b). After 4-6 min the character of respiratory unit activity changed sharply: the volleys became shorter, they contained fewer spikes, and the frequency of the volleys was increased (Fig. 3c). The pulmonary ventilation was increased by 200-300% compared with the initial level, initially through deepening and later through quickening of respiration. Despite the more intensive hyperventilation, pCO_2 in the arterial blood was kept between 45 and 58 mm Hg (initial pCO_2 29-32 mm Hg), and pH fell to 7.21-7.17. The blood oxygen saturation and pO_2 differed only a little from the values recorded during hypoxia with 2% CO_2. Consequently, on the addition of 5% CO_2 to the hypoxic gas mixture the efficiency of pulmonary ventilation fell sharply and hypercapnia and respiratory acidosis ensued. The developing respiratory acidosis led to the appearance of incompletely oxidized products of metabolism in the blood and, consequently, to the development of metabolic acidosis. The blood supply and metabolism of the brain and the affinity of hemoglobin for oxygen, as previous investigations showed, are reduced under these conditions [1, 5, 7, 8]. This is the likely explanation of the inhibition of unit activity of the bulbar respiratory neurons and the low efficiency of the pulmonary ventilation during inhalation of a hypoxic gas mixture with 5% CO_2.

Comparative analysis of the electrophysiological data and of the indices of external respiration and the blood gas composition lead to the conclusion that both hypocapnia and hypercapnia in acute hypoxia adversely affect unit activity of the bulbar respiratory neurons.

The results of these investigations showed clearly that it is only when during the action of hypoxia pCO_2 of the arterial blood was maintained at the normocapnic level (by the addition of 2% CO_2) that a stable level of increased, rhythmic discharge of volleys of spikes by the bulbar respiratory neurons was observed. Increased volley activity of the bulbar respiratory neurons determined both the rhythmic character of the respiration and the high level of pulmonary ventilation; consequently, pO_2 in the alveoli and in the arterial blood was increased.

The beneficial effect of addition of 2% CO_2 to the hypoxic gas mixture was evidently due also to the fact that under those conditions mechanisms of regional redistribution of blood are activated, so that the blood flow to such vitally important organs as the brain and heart and the pO_2 level in them are increased [5, 8, 9, 11, 12].

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