EXTERNAL RESPIRATION AND FUNCTIONAL STATE OF THE RESPIRATORY CENTER IN HYPOXIA DEVELOPING AFTER INACTIVATION OF CARBONIC ANHYDRASE

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In experiments on cats, inactivation of carbonic anhydrase by acetazolamide (Diamox) prevented the development of hypocapnia and associated disturbances of the firing pattern of respiratory neurons in acute hypoxia. However, comparison of the electrophysiological data, the indices of external respiration and the acid–base balance, and pO_2 and pCO_2 of arterial blood showed that, while preventing the development of pathological respiration of Cheyne–Stokes type during hypoxia, inactivation of carbonic anhydrase by Diamox causes dissociation of thoracic and abdominal respiration and dyspnea. Changes in metabolic processes and disturbance of electrolyte balance at the cellular level also contribute to the development of dyspnea.

KEY WORDS: hypoxia; Diamox; external respiration; respiratory center.

A state of steady normocapnia during hypoxia can be produced by inhibiting carbonic anhydrase activity means of Diamox (acetazolamide) [2, 6, 11]. The rate of hydration of CO_2 in the tissues and dehydration of carbonic acid in the lungs is thereby reduced, so that pCO_2 in the tissues and blood is increased and ventilation of the lungs stimulated. This delays the fall in pO_2 in the blood and tissues and restores pCO_2 to normal. This state lasts 3-4 h after the administration of Diamox and can be maintained for days by repeated doses of the compound [4, 5]. Diamox has been recommended for prevention of hypocapnia and the subsequent respiratory disorders in persons climbing at high altitudes or during high-altitude flights [3,4,8]. The effect of Diamox in man and also in animals has been considered to provide a different approach to the problem of adaptation to hypoxia [6].

The functional state of the respiratory center and the mechanism of the increased pulmonary ventilation were studied during hypoxia developing after inactivation of carbonic anhydrase by Diamox.

EXPERIMENTAL METHOD

Cats were anesthetized with pentobarbital (30-40 mg/kg, intraperitoneally). Action potentials of bulbar respiratory neurons (Szentagothai's atlas) were recorded by microelectrode and stereotaxic techniques. The metal microelectrode had a tip 1-3 μ in diameter. Parallel recordings were made of the EMG of the diaphragm and intercostal muscles, the pneumogram, indices of external respiration and the acid–base balance, and the partial pressures of the arterial blood gases (by the Astrup–Siggaard–Andersen method). Hypoxia was produced in the animals by replacing the air by a mixture of 10% O_2 and 90% N_2; 550 mg Diamox was injected intraperitoneally.

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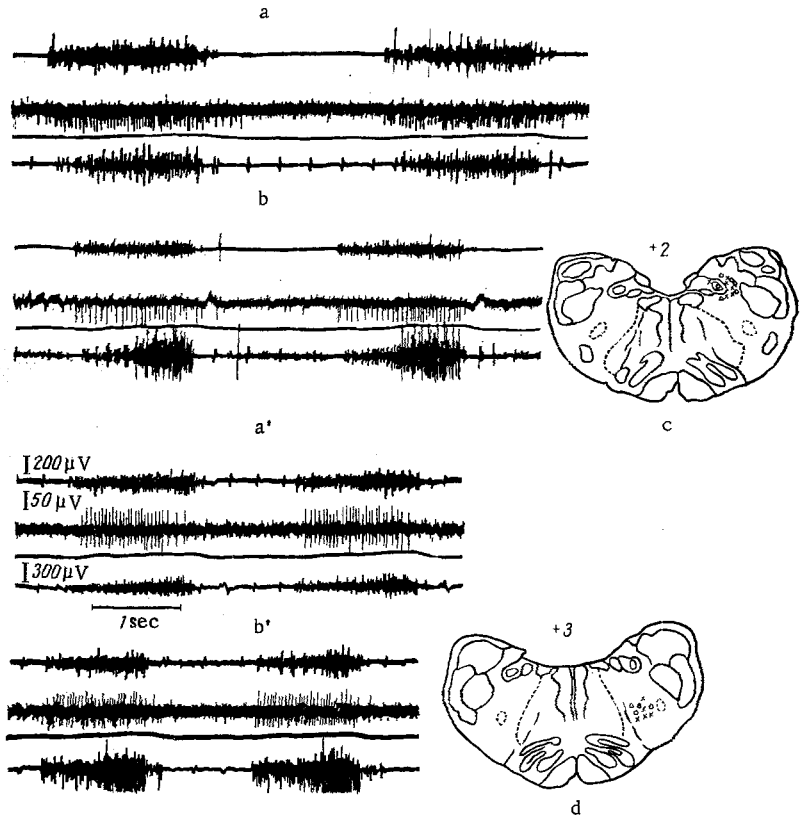

Fig. 1. Unit activity of inspiratory bulbar neurons and EMG of respiratory muscles before (a, a') and 40 min after (b, b') injection of Diamox, and frontal sections through medulla of cat showing localization of respiratory neurons at levels of +2 and +3 mm rostrally through the obex (c, d; ○ "above – " inhibitory," ○ below – "excitatory"; ×-bulbo – spinal neurons after Bianchi). Records (from top to bottom): EMG of diaphragm, unit activity of bulbar respiratory neurons, pneumogram, EMG of intercostal respiratory muscles.

TABLE 1. Gas Pressures and Indices of Acid–Base Balance of Arterial Blood of Anesthetized Cats in Hypoxia before and after Injection of Diamox (M ± m)

Index	Experimental conditions				
	Control	30 min after injection of Diamox	40 min after injection of Diamox and 10 min after beginning of inhalation of 10% O_2–90% N_2 mixture	10 min after beginning of inhalation of 10% O_2–90% N_2 mixture	50 min after beginning of inhalation of 10% O_2–90% N_2 mixture and 40 min after injection of Diamox
Respiration rate (per minute)	25,0±0,7	29±0,09	30,0±1,0	25,0±1,1	26,0±1,2
Pulmonary ventilation (in ml/min)	375,0±27,0	730,0±60,0	800,0±62,5	625,0±46,3	700,0±65,0
pH	7,37±0,001	7,31±0,002	7,35±0,002	7,41±0,002	7,30±0,001
pCO_2 (in mm Hg)	37,0±1,8	32,0±1,0	30,0±1,1	23,5±1,3	28,0±1,1
pO_2 (in mm Hg)	104,0±2,5	118,0±3,0	90,0±2,8	52,0±2,7	72,0±2,1
O_2 saturation of arterial blood (in %)	91,0±1,0	98,0±1,0	84,0±2,4	62,0±2,1	82,0±2,9
Buffer base shift (in meq/liter) liter)	–3,0±0,73	–9,6±0,66	–8,4±0,73	–6,4±0,66	–10,5±0,87
True bicarbonate (in meq/liter)	19,5±0,66	15,9±0,43	14,6±0,49	17,0±0,67	15,0±0,86

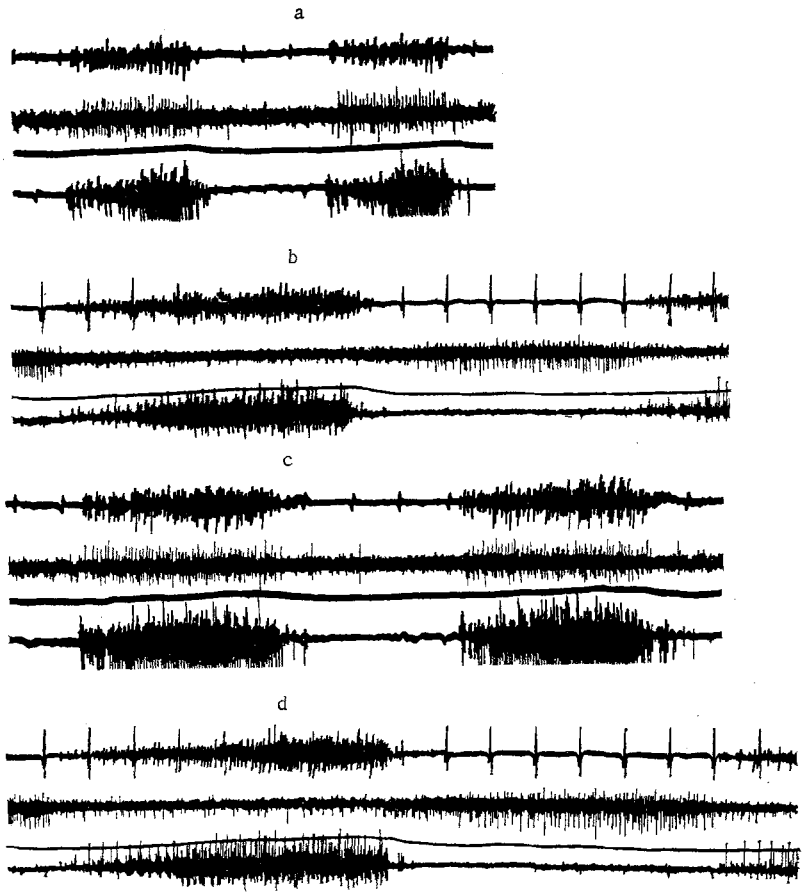

Fig. 2. Unit activity of inspiratory (a) and expiratory (b) bulbar neurons and EMG of respiratory muscles 40 min after injection of Diamox (c) and during inhalation of hypoxic gas mixture following injection of Diamox (d). Arrangement of records as in Fig. 1.

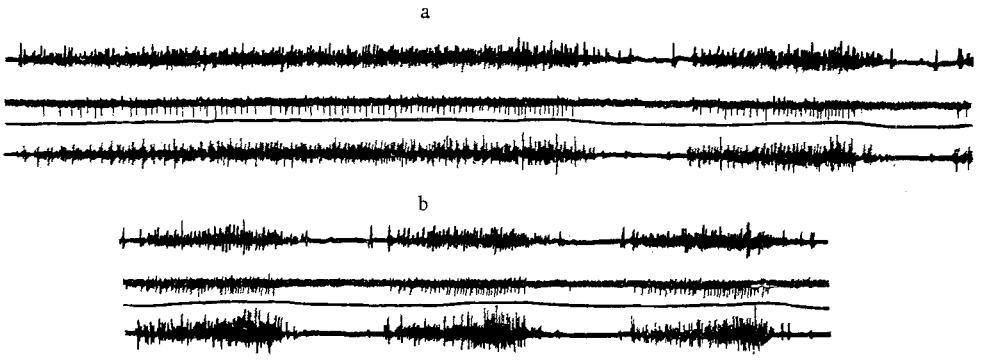

Fig. 3. Unit activity of inspiratory bulbar neurons and EMG of respiratory muscles during inhalation of hypoxic gas mixture (a) and 40 min after injection of Diamox during hypoxia (b). Arrangement of records as in Fig. 1.

EXPERIMENTAL RESULTS AND DISCUSSION

From 20 to 30 min after injection of Diamox into the animal, when the respiration rate was slightly increased, the minute volume of pulmonary ventilation was 1.5-2 times higher than initially. Because of the increased pulmonary ventilation, oxygenation and pO_2 of the arterial blood were increased whereas pCO_2 remained within the initial limits. Despite the normocapnia, a shift of the acid–base balance of the blood occurred toward metabolic acidosis (Table 1). Activity of the inspiratory neurons connected with motoneurons of the diaphragm was definitely lowered whereas activity of the inspiratory neurons connected with the motoneurons of the intercostal muscles was sharply increased. These two groups of neurons corresponded in function and localization to the bulbo-spinal neurons described by Bianchi [1]. Marked dissociation of thoracic and abdominal respiration was observed. The high level of pulmonary ventilation was maintained chiefly by an increase in electrical activity of the intercostal muscles and by increased thoracic respiration (Fig. 1).

Against this background a hypoxic gas mixture, which the animals inhaled for 10-20 min, caused a further increase in pulmonary ventilation (Table 1), due to an increase in activity of both inspiratory and expiratory bulbar neurons (Fig. 2). Disturbance of reciprocal connections between the inspiratory and expiratory groups of neurons can be regarded as an adaptive response of the respiratory apparatus to hypoxia. Characteristically, increased afferentation from the carotid sinus reflexogenic zones during hypoxia did not abolish the dissociation of thoracic and abdominal respiration arising after the injection of Diamox. Increased activity of the intercostal respiratory muscles could be maintained by this afferentation, for the carotid chemoreceptors are connected with bulbar respiratory neurons related to motoneurons of the intercostal muscles [7].

Thanks to hyperventilation the metabolic acidosis, which developed after injection of Diamox, was largely compensated by respiratory alkalosis. The fall in the bicarbonate concentration under these conditions prevented an alkaline shift of pH, thereby reducing the inhibitory effect of the low hydrogen-ion concentration on peripheral chemoreceptors. Maintenance of pCO_2 at the normocapnic level during hypoxia ought to have led to an improvement in the cerebral blood flow, shifted the oxyhemoglobin dissociation curve to the right, and so increased pO_2 in the brain tissues [9-10]. All these effects would probably have resulted in an absence of disturbance of the firing pattern of the neurons even during prolonged hypoxia: Regular respiration was maintained throughout the experiment. Further investigations showed that even when the animals were exposed to acute hypoxia and developed a marked disorder of their respiratory rhythm, injection of Diamox restored the previous rhythm of unit activity and normal respiration (Fig. 3). This was considerably facilitated by the compensation of respiratory alkalosis (Table 1). A shift of pH to the acid side caused a further increase in pulmonary ventilation and in pO_2 of the arterial blood, whereas pCO_2 was maintained within close to normocapnic limits.

The beneficial effects of inactivation of carbonic anhydrase during hypoxia suggest, at first glance, that the use of Diamox can be recommended. However, although Diamox prevents the development of periodic respiration of the Cheyne–Stokes type, it dissociates thoracic and abdominal respiration, and this may lead to dyspnea. Under these conditions the transport of blood gases also is modified, the fraction of the CO_2 molecules that combines with hemoglobin to form carbamino compounds is increased [5], and it is therefore difficult to accept the view that administration of Diamox can alter the approach "to the problem of adaptation to hypoxia" [6].

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