HYPERVENTILATION HYPOCAPNIA AND MUSCLE TONE

S. I. Frankshtein and L. N. Sergeeva

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KEY WORDS: hyperventilation hypocapnia; apnea; decerebrate rigidity.

It is almost generally accepted that in the waking state hyperventilation hypocapnia does not cause apnea. Indeed, it may lead to paradoxical polypnea [2]. Fink et al. [4] first showed that hyperventilation apnea arises in unanesthetized animals only after decerebration at the intercollicular level of the brain stem. Since that time many investigations of hyperventilation apnea have been conducted on decerebrate animals.

Decerebration at the intercollicular level of the brain stem gives rise to decerebrate rigidity in the animal — a sharp increase in postural tone — tone of the extensor muscles which counteract the earth's force of gravity. However, no comparative investigation of hyperventilation hypocapnea has hitherto been carried out on tone of the respiratory and nonrespiratory muscles. The present investigation was devoted to study of this problem.

EXPERIMENTAL METHOD

Experiments were carried out on 10 cats. Decerebration at the intercollicular level was performed by Sherrington's method. The animals were artificially ventilated under positive pressure (volume 50 cm^3, frequency 65 respiratory movements/min); pCO_2 was reduced to 15-20 torr. Electrical activity was recorded in m. triceps, an extensor of the forelimb, and the inspiratory muscles — the interchondrial part of the intercostal muscles and the sternal part of the diaphragm. The vagus nerves were divided in the neck.

EXPERIMENTAL RESULTS

Between 30 sec and 1 min after the beginning of hyperventilation of the lungs the inspiratory volleys decreased and disappeared. Instead of them, tonic activity was recorded in the intercostal muscle or diaphragm, and sometimes in both (Fig. 1).

Tone in the nonrespiratory muscles also increased sharply at the same time. In the decerebrate cat, fixed on its back, the limbs, especially the forelimbs, were even more outstretched, and electrical activity was correspondingly increased in m. triceps, an extensor of the arm (Fig. 1). Vagotomy did not affect the experimental results.

However, the picture changed sharply with the ending of artificial ventilation of the lungs. Tonic activity in the respiratory muscles was preserved throughout the period of apnea (up to 1-2 min), whereas tone in the limb muscles disappeared almost at once and was replaced by hypotonia (Fig. 1). The limbs were lightly flexed and remained in the position in which they were placed.

Hypocapnia alone thus caused not an increase, but a reduction in postural tone in the nonrespiratory muscles. Enhancement of tonic activity observed in them during hypocapnia was caused by a reflex mechanism, by impulses from receptors in the chest arising during artificial hyperventilation.

As was mentioned above, after division of the vagus nerves, artificial ventilation of the lungs continued to strengthen activity in the nonrespiratory muscles. Hence, it follows that the increase of activity in those muscles was due to afferent impulses, not from the lungs, but from receptors of the respiratory muscles and joints. With the end of artificial ventilation, postural tones disappeared in the nonrespiratory muscles.

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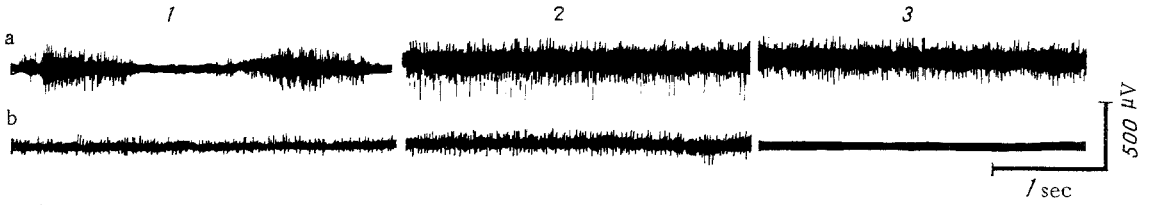

Fig. 1. Electromyograms of an inspiratory intercostal muscle (a) and of m. triceps (b). 1) Before, 2) during hyperventilation (tonic activity in intercostal muscles and m. triceps), 3) after stopping hyperventilation, tonic activity persists in the intercostal muscle but disappears in m. triceps.

It was postulated previously that hyperventilation apnea is characterized by absence of activity in the respiratory muscles. Later, with the development of electromyography, it was found that hyperventilation hypocapnea induces tonic electrical activity in inspiratory or in expiratory muscles or in both together [1]. Analysis of the above data suggests that hypocapnea causes, not an increase, but a decrease in tone in the repiratory muscles (just as in nonrespiratory muscles). Tonic activity recorded in them during hyperventilation apnea is in fact also maintained artificially — by an additional tonic stimulus arising from the respiratory center itself.

Hyperventilation hypocapnia thus causes rhythmic activity of respiratory neurons to change into continuous tonic activity [1]. The mechanism of this phenomenon is not yet clear. Comparative investigation of the effect of hyperventilation hypocapnia on respiratory and nonrespiratory muscles will help to elucidate it.

Decerebrate rigidity is caused by disinhibition of neurons by the brain-stem reticular formation. As was shown above, hypocapnia inhibits decerebrate rigidity. Hence it follows that hypocapnia leads to inhibition of neurons of the reticular formation which maintain decerebrate tone. This conclusion is in full agreement with the fact that hyperventilation causes synchronization of electrical activity in the cerebral cortex also, and this can also be explained by depression of activity of reticular neurons [5].

Respiratory neurons are located in the brain-stem reticular formation. It is generally accepted that the rhythm of respiratory neurons is caused by periodic inhibition of their natural tonic activity [3]. The results of the present experiments suggest that an important role in this periodic inhibition is played by nonrespiratory neurons of the reticular formation. Depression of their activity also causes continuous activity of respiratory neurons, and the latter gives rise to tonic activity of the respiratory muscles.

Hyperventilation hypocapnia thus causes a reduction and not an increase in tone in both nonrespiratory and respiratory muscles. However, against this background reflex excitability is increased. As a result, under the influence of impulses from receptors of the respiratory muscles and of the joints, arising during hyperventilation, paroxysmal tonic activity is enhanced in the nonrespiratory muscles. In respiratory muscles during hyperventilation apnea, this tonic activity arises as the result of continuous tonic activity from the respiratory center.

These results are in full agreement with clinical observations showing that hyperventilation hypocapnia causes an increase in reflex muscle excitability. For instance, hyperventilation hypocapnia has been used for a long time for diagnostic purposes to provoke an epileptic fit [5]. Seizures have been described in patients with the "hyperventilation syndrome." Hyperventilation also causes increased tendon reflexes [6].

The results of the present investigation suggest that this increase in reflex excitability under clinical conditions probably arises against the background of preliminary depression of postural tone, caused by hyperventilation hypocapnia.

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EFFECT OF ANTITUBULIN ANTIBODIES ON ACTIVITY OF THE TASTE RECEPTOR APPARATUS

A. I. Esakov and O. D. Meshcheryakova

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The attention of research workers has recently been increasingly drawn to the functional role of the cytoplasmic tubulin—microtubules complex in mechanisms of sensory reception [7]. Depression of responses to stimulation has been demonstrated on olfactory [8] and mechanically sensitive receptors [11, 15] of certain invertebrates to stimulation after treatment with colchicine or vinblastine, pharmacological agents connected with tubulin and, consequently, destroying microtubules [16].

The present writers showed previously on chemoreceptors of the frog tongue that colchicine causes a sharp decrease in their sensitivity, so that afferent impulse generation may cease completely [1]. This effect was shown to be reversible under the influence of substances leading to an increase in the intracellular cAMP level: cAMP, dibutyryl-cAMP, the phosphodiesterase inhibitor theophylline, adrenalin, and GTP [2], and also during activation of the sympathetic nervous system [3]. The specificity of the restorative action of cAMP was demonstrated because inactive forms of nucleotides 2',3'-cAMP and 5'-AMP were ineffective and did not restore responses of the tongue chemoreceptors blocked by colchicine. Administration of cGMP or acetylcholine as a rule potentiated the effect of colchicine. The results were evidence of the importance of the colchicine-sensitive and cAMP-dependent process in maintenance of the chemosensitive function of the receptors. However, the nature of this process remained unexplained because the spectrum of action of colchicine is rather wide. It could not only interact specifically with tubulins, leading to destruction of the microtubular apparatus, but could also interfere with the course of various processes: inhibit nucleic acid and protein synthesis [9], inhibit energy metabolism [10], and block intracellular transport of materials [13] and activity of individual enzymes [6, 14].

To test the hypothesis that the tubulin—microtubules system plays an essential role in the mechanisms of function of the tongue chemoreceptors, in the investigation described below the effect of selective disturbances of this system, caused by means of purified monospecific antitubulin antibodies, was studied.

EXPERIMENTAL METHOD

Antitubulin antibodies were isolated from total fractions of immunoglobulins from a rabbit injected with purified tubulin. The method of immunosorption of tubulin, immobilized on Biogel P-300 by the method in [17], on a column was used. The nonimmune fraction of γ-globulins, not containing antitubulin antibodies, and also antibodies against specific nerve tissue proteins (S-100, GP-25) were used as the control. Antitubulin antibodies were injected subepithelially into the tongue in a dose of 0.2 mg/ml and in a volume of 0.2 ml.

The indicator of activity of the taste receptors was the spike discharge recorded from fibers of the glossopharyngeal nerve of the frog *Rana temporaria* by means of silver electrodes on a C-9 oscilloscope (from Nihon Kohden, Japan). A 0.5 M solution of NaCl, a 1.0 M solution of glucose, and tap water, which was applied to the dorsal surface of the tongue in a volume of 6.0 ml, were used as taste stimuli. Recording was carried out for 10 sec, after which the tongue was rinsed with Ringer's solution.

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