MICROELECTROPHYSIOLOGICAL ANALYSIS OF UNIT ACTIVITY OF THE MEDULLARY RESPIRATORY CENTER IN BOTULINUS POISONING

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Electrical activity of different types of medullary respiratory neurons was recorded extracellulary in cats and rabbits poisoned with botulinus toxin. During the development of a general paralytic syndrome of botulism and paralysis of respiration all types of medullary respiratory neurons preserve their activity and its parameters differed only slightly from the control.

The generalized paralytic syndrome in botulinus poisoning develops, according to some observations, as a result of the blocking of conduction in myoneural synapses [11], while according to others it results from the selective pathogenic action of the toxin on large motoneurons in the anterior horns of the spinal cord [7]. Paralysis of the respiratory muscles, on the other hand, is frequently regarded as the result of a disturbance of activity primarily of the medullary respiratory centers [1, 2, 12]. The writer has previosly shown that paralysis of the respiratory muscles arises primarily through inhibition of activity of the spinal respiratory motoneurons while the transmission of information from the bulbar respiratory centers remains intact [8].

This paper describes the results of a study of the character of electrical discharges of cells of the bulbar respiratory center in the various stages of botulinus poisoning, including in the phase of complete cessation of spontaneous respiration.

EXPERIMENTAL METHOD

Experiments were carried out on cats and rabbits of both sexes weighing 2–3 kg and poisoned by intravenous injection of type B botulinus toxin in a dose of 2.5 mg/kg (1 MLD for mice = 0.00001 mg of the dried toxin). In cats a generalized paralytic syndrome usually developed 15–18 h after poisoning, and in rabbits 3–3.5 h thereafter. Artificial respiration was applied to the poisoned animals at the stage of cessation of spontaneous external respiration. Experiments with intracellular recording of the discharges of bulbar respiratory neurons were carried out under Nembutal (30 mg/kg) or urethane (1.5 g/kg) anesthesia by the usual method [10]. Simultaneously with recording of unit activity of the respiratory neurons, the pneumogram was recorded by means of a thermistor transducer mounted in the cannula of a tracheotomy tube. Both processes were recorded on a type N-102 loop oscillograph.

Altogether the activity of 180 respiratory neurons in rabbits and 358 neurons in cats were recorded, but electrical activity only of inspiratory and expiratory neurons was analyzed by plotting histograms. Histograms of the distribution of frequencies in the discharges of the respiratory volleys (in spikes/sec), of their absolute duration (in seconds), and of the ratio between the time interval of the volley and the period of the respiratory cycle (relative duration) were plotted.

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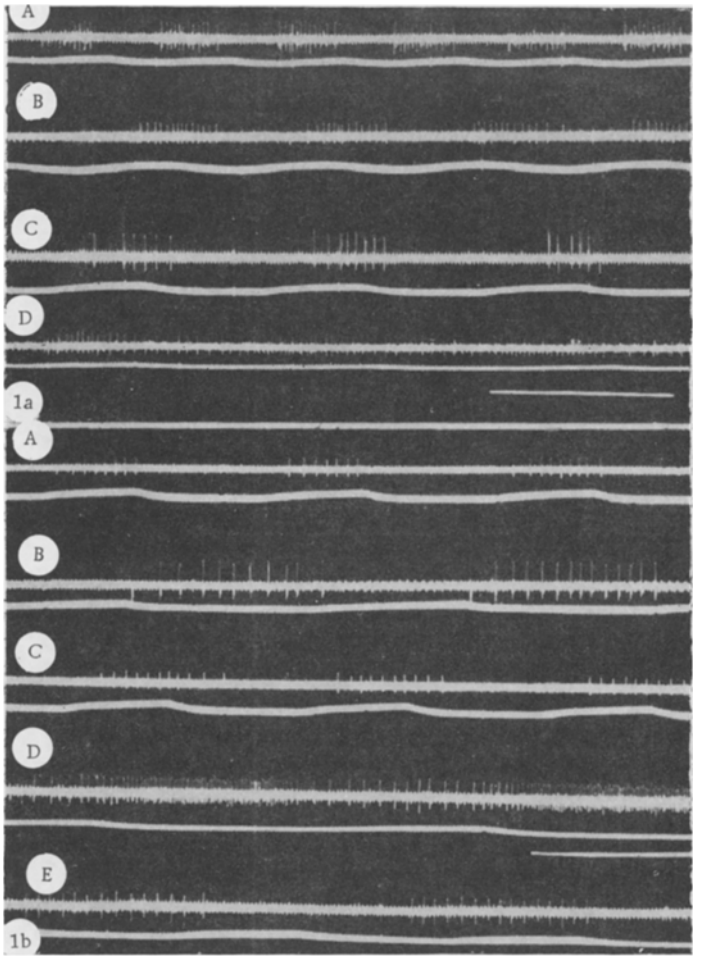

Fig. 1. Record of electrical discharges of respiratory neurons of a rabbit with generalized botulinus paralysis, maintained on artificial respiration: A) inspiratory neurons; B) expiratory neurons; C) inspiratory-expiratory neurons; D) neuron with continuous activity; E) inspiratory neuron after bilateral vagotomy. Legend: top line denotes discharges of respiratory cells, bottom line pneuogram (inspiration upward). Time marker 1 sec.

EXPERIMENTAL RESULTS

Unit activity of the medullary respiratory neurons were studied in rabbits and cats, i.e., in animals of species with high and low sensitivity to botulinus toxin, respectively. Four types of respiratory neurons could be identified in both species of poisoned animals during the development of severe dyspnea in association with a generalized paralytic syndrome, and, finally, after complete blocking of external respiration, in the region of the bulbar respiratory center (just as under normal conditions [3]): inspiratory neurons, expiratory neurons, neurons with continuous activity modulating the firing rate with the phases of the respiratory cycle, and "boundary" neurons, firing only at the boundary between the phases – inspiratory-expiratory and expiratory-inspiratory (Fig. 1a, b). Among the inspiratory and expiratory neurons, variations were found in the duration of the volley, the time of its beginning and end relative to the corresponding phase of respiration, and the number of spikes in the volley and the point at which the firing rate reaches its maximum. Similar variations have been observed in normal animals [4].

As the histograms (Fig. 2) show, in cats with botulinus poisoning the development of external respiratory failure coincided with some increase in firing rate mainly of the inspiratory neurons and shortening of the absolute duration of the respiratory volleys in nerve cells of both types. The parameters of relative

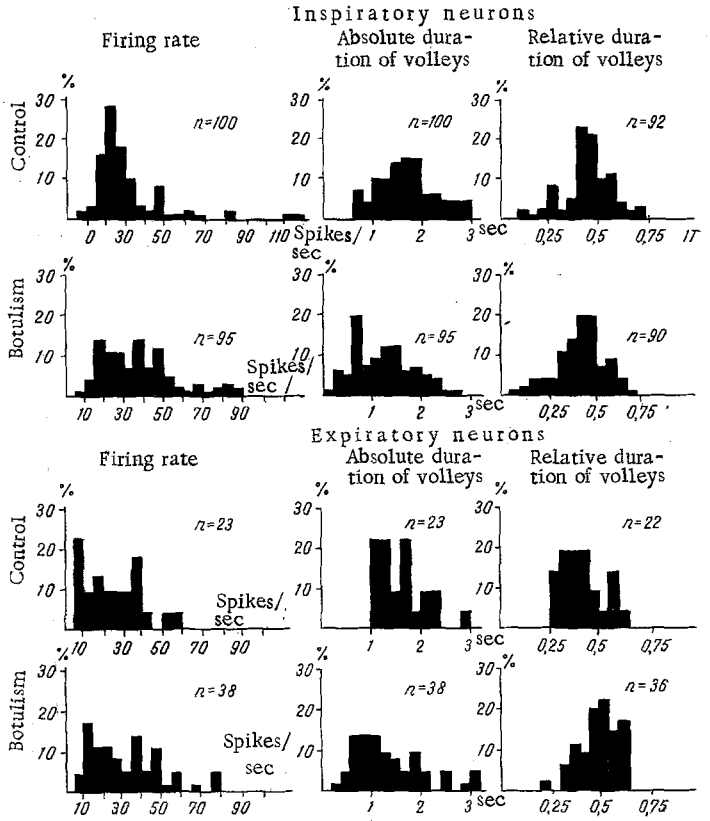

Fig. 2. Histograms of inspiratory and expiratory neurons of bulbar respiratory center in cats under normal conditions and in botulinus poisoning.

duration of the volleys showed no significant changes. So far as the mechanism of the disturbances of activity of the respiratory neurons is concerned, they can evidently be regarded as the result of the action of hypoxia developing in severe botulism because of inhibition of the motor activity of the respiratory muscles [6, 8]. Hypoxia, however, usually leads to an increase in the firing rate of the inspiratory neurons, shortening of the duration of the respiratory volleys, and preservation of the normal ratios between their duration and the interval of the respiratory cycle [3, 4, 9].

In cats, in which botulinus poisoning develops comparatively slowly, with a protracted period of onset of severe external respiratory failure, the cells of the bulbar respiratory center thus not only discharged rhythmically throughout the period of poisoning, but they also remained capable of responding to an oxygen deficiency in the body. Rhythmic discharges of the respiratory neurons were recorded in the cats even after the end of spontaneous respiration, and when it had been briefly restored a few minutes after artificial ventilation of the lungs. Systematic connection of the animals to the artificial respiration apparatus delayed the irreversible inhibition of spontaneous respiratory movements for many hours (6 h or more). This feature distinguishing the course of botulinus poisoning in cats, because of the limited duration of the acute experiment, did not allow unit activity of the bulbar respiratory center to be investigated during the period of final respiratory arrest. This was an argument in favor of analogous experiments on rabbits, in which all stages of botulinus poisoning, including irreversible total paralysis of the skeletal muscles, developed within a short period of time (2-3 h).

In these cases, it was possible to investigate unit activity of the bulbar respiratory neurons for many hours during the complete absence of spontaneous respiration when the animals were kept alive purely by artificial ventilation of the lungs. During the development of total paralysis of the skeletal and respiratory muscles in rabbits, the rhythmic discharges of the respiratory neurons corresponded to the phases of artificial respiration (Fig. 1b). As the histograms (Fig. 3) show, under these circumstances the firing rate of the inspiratory neurons was somewhat reduced while that of the expiratory neurons was increased. Cells with an expiratory firing rate were observed somewhat more frequently than usually in the control [4, 9].

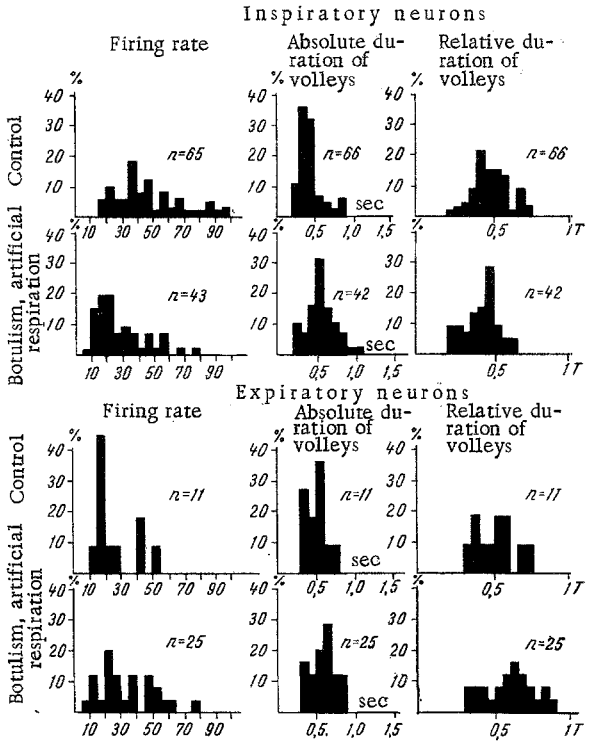

Fig. 3. Histograms of inspiratory and expiratory neurons of the bulbar respiratory center in rabbits under normal conditions and in botulinus poisoning associated with the cessation of spontaneous respiration. Abscissa for Firing rate, pulses/sec.

Presumably these changes appeared because of the application of artificial respiration to the animal [5]. During this period bilateral vagotomy preserved the volley activity of the inspiratory and expiratory neurons and, just as under normal conditions, it led to the prolongation of their volleys [4, 9].

It can be concluded from the results of these experiments that the development of total botulinus paralysis leads to respiratory arrest despite the preservation of all types of rhythmic discharges of the bulbar respiratory neurons. Information arriving from the cells of the respiratory center during paralysis of the respiratory muscles is evidently quite sufficient to cause excitation of the motoneurons of the respiratory muscles. This is shown by the fact that the slower development of the lesion to the nucleus of the phrenic nerve on the side of preliminary hemisection of the spinal cord appreciably prolongs the survival of an animal poisoned with a lethal dose of botulinus toxin: because of activation of the crossed reticulospinal tracts, contractions of the diaphragm recover on the side of hemisection of the spinal cord. In this way spontaneous external respiration can take place even when all other regions of the skeletal muscle are paralyzed [8].

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