MECHANISM OF THE RESPIRATORY PARALYSIS IN BOTULISM, TETANUS, AND DIPHTHERIA

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Clinical and experimental investigations [1-4, 6, 7, 10, 12] have revealed considerable changes in the function of the respiratory apparatus in botulism, tetanus, and diphtheria. It has been suggested that the cause of death in these neurotoxicoses is paralysis of the respiratory centers. Meanwhile, it has not yet been explained whether neurotoxins have a paralytic action on the cells of the respiratory centers. The mechanisms of their action on the conducting pathways and on the motor neurons of the respiratory muscles have been studied even less adequately.

The object of the present study was to investigate the pathogenic action of the toxins of botulism, tetanus, and diphtheria on the various links of the nervous apparatus of respiration: on the respiratory centers with the descending conducting pathways and on the spinal motor centers of the respiratory muscles.

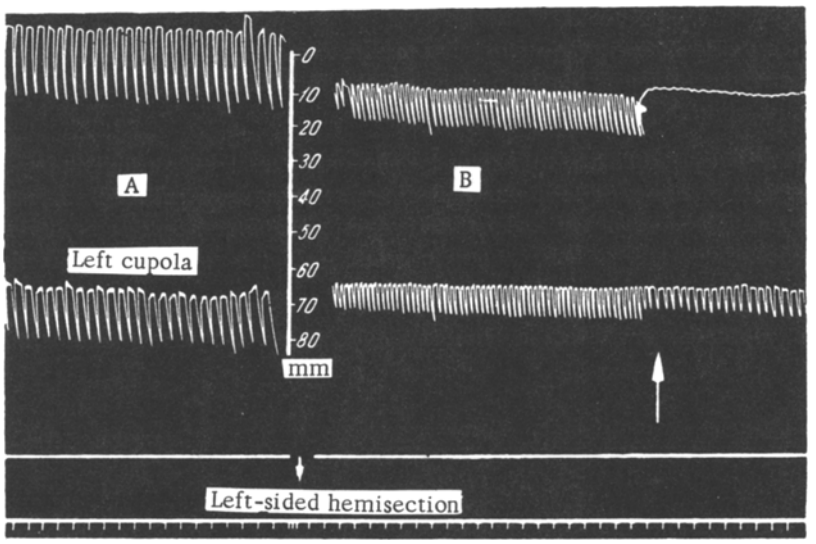

Fig. 1. Absence of paralysis of diaphragm on the side of hemisection of spinal cord in a cat poisoned with botulism toxin. Marked paralytic syndrome. Contractions of cupolas of the diaphragm before (A) and after (B) hemisection of the spinal cord on the left side. The arrow indicates division of the right phrenic nerve. Below) time marker (5 sec).

EXPERIMENTAL METHOD

Experiments were performed on cats and dogs poisoned with the toxins of botulism type A (1 MLD for mice, 0.00001 mg dried toxin), tetanus (1 MLD, 0.000081 mg), and diphtheria (1 MLD for guinea pigs, 0.003 ml). A generalized neurotoxicosis was obtained in cats by intravenous injection of the toxins in the following doses: botulism 0.05-0.1 mg/kg body weight, tetanus 0.1-0.5 mg/kg, and diphtheria 0.001 ml/kg. "Local" lesions to one cupola of

the diaphragm were produced by intramuscular injection of the toxins in the following doses: botulism 0.05-0.1 mg/kg body weight, tetanus 0.1-0.5 mg/kg and diphtheria 0.001 ml/kg. In dogs, local forms of neurotoxicosis were obtained by injection of the toxins into the nerve trunk in the following doses: botulism 0.05-0.1 mg/kg body weight, tetanus 0.05-0.08 mg/kg.

Acute experiments were carried out on poisoned and nonpoisoned animals under urethane anesthesia (1 g/kg). The respiratory movements were recorded by means of a Marey's capsule connected to a cuff or to the tracheotomy tube. The contractions of the cupolas of the diaphragm were recorded separately by means of two isotonic myographs. Respiratory reflexes were evoked by stimulation of the central end of the divided vagus nerve in the neck with rectangular pulses of current from a generator (length of pulses 0.65 millisec, frequency 1-500/sec). The crossed phrenic phenomenon was evoked by the method described in many previous papers [11-16].

Altogether 116 cats and 50 dogs were used in the experiments, 15 of the cats and 21 of the dogs acting as controls.

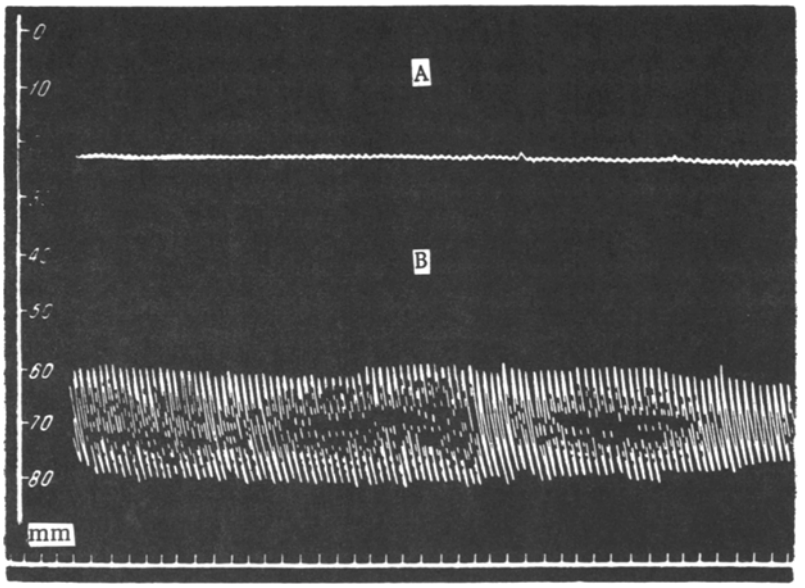

Fig. 2. Absence of paralysis of diaphragm on the side of preliminary hemisection of the spinal cord in a cat poisoned with botulism toxin. Generalized paralytic syndrome. A) Paralysis of cupola of diaphragm on intact side; B) contractions of cupola of diaphragm on the side of preliminary hemisection of the spinal cord. Below) time marker (5 sec).

EXPERIMENTAL RESULTS

After hemisection of the spinal cord above the nuclei of the phrenic nerve the contractions of the paralyzed cupola of the diaphragm could be restored by blocking or dividing the phrenic nerve on the opposite side. This restoration is the result of the bringing into play of crossed connections between the intact inspiratory reticulospinal fibers and the motor nucleus of the phrenic nerve on the side of the hemisection [11-16]. This phenomenon, the crossed phrenic phenomenon, was used to analyze the mechanism of action of the bacterial neurotoxins on the various links of the nervous apparatus of respiration. In the first series of experiments we investigated the functional state of the respiratory center and conducting pathways on the side of a local lesion of the diaphragm caused by the toxins of botulism, tetanus, and diphtheria. For this purpose, to obtain the crossed phrenic phenomenon, hemisection of the spinal cord was performed on the sound side and division of the phrenic nerve on the affected side.

In 13 experiments on cats and dogs carried out on the fifth-twenty-first day after poisoning with botulism toxin no change was found in the function of the respiratory center and the conducting pathways on the side of the paralyzed cupola of the diaphragm: a crossed phenomenon was observed in every experiment.

The results of the other 49 experiments on cats and dogs with local tetanus of the diaphragm showed that the crossed phrenic phenomenon readily occurred on the sixth-seventh day after poisoning, and, as a rule, disappeared later

(during the second-third week). Similar results were obtained in the 29 experiments on cats with local diphtheria of the diaphragm: a crossed phenomenon was observed during the first 12 days after poisoning and was absent on the twentith-twenty-second day.

Hence, the results of experiments in which various local neurotoxicoses were reproduced showed that certain differences occurred in the mechanism of the lesion of the nervous apparatus supplying the diaphragm: in botulism the pathological process was apparently limited to the motor neurons of the phrenic nerve regardless of the stage of poisoning, whereas the comparatively rapid disappearance of the crossed phenomenon in tetanus and diphtheria indicated more complex disturbances, probably affecting more than one link of the nervous apparatus of respiration.

In the second series of experiments the object was to discover whether the crossed connections between the inspiratory reticulospinal tracts and the motor nuclei of the phrenic nerve take part in the processes of compensation of respiratory failure developing in the course of severe, generalized forms of botulism, tetanus, and diphtheria.

In 8 experiments on cats receiving tetanus toxin and in 5 on cats receiving diphtheria toxin the crossed phrenic phenomenon was found to be preserved in every case, even during the development of a very severe toxicosis. It was similar in character to that observed in the controls. In analogous experiments with botulism toxin, when the ordinary technique was used to reproduce it, a crossed phrenic phenomenon was observed only in the presence of a mild lesion (mild pareses of the skeletal muscles). If a more marked paralytic syndrome of botulism was present, in all 17 experiments hemisection of the spinal cord was not accompanied by the usual unilateral paralysis of the diaphragm (Fig. 1). The appearance of a crossed phrenic syndrome without division of the phrenic nerve on the opposite side undoubtedly meant that considerable activation of the crossed connections had occurred, and that these connections were concerned in the mechanism of compensation of the respiratory insufficiency arising in severe botulism.

The correctness of this conclusion was confirmed by experiments in which the phrenic nerve was divided on the side opposite to that of hemisection of the spinal cord. In these conditions, in 7 of the 17 experiments described above, the contractile activity of the functioning half of the diaphragm began to disappear 30-150 sec after division of the nerve, decompensation of respiration developed, and the animal invariably died unless artificial respiration was performed. After a short time interruption of artificial respiration again led to restoration of the contractions of the diaphragm on the side of hemisection of the spincal cord for a short time. The results suggest that in botulism, paralysis of the diaphragm does not result from exclusion of the activity of the respiratory center and conducting pathways, but from a sharp fall in the excitability and functional capacity of the motor neurons of the phrenic nerve nuclei.

This latter hypothesis formed the basis of the third series of experiments, the object of which was to investigate the function of the nervous apparatus of respiration during the action of the toxins of botulism, tetanus, and diptheria on the nuclei of the phrenic nerves, applied at different times. The starting point of the argument was that injury to nervous centers by bacterial neurotoxins may be considerably delayed if they are in a state of inhibition [5, 9]. Prolonged inhibition of one phrenic nerve nucleus was produced by hemisection of the spinal cord at the level of the 2nd cervical vertebra: the function of the diaphragm on the intact side was not disturbed in the cats, but on the paralyzed side it could be restored only by activation of the crossed connections. Animals prepared in this manner were poisoned, as in the previous experiments, with lethal doses of toxins of botulism, tetanus, and diptheria. Altogether 22 experiments with generalized botulism, 15 experiments with tetanus, and 11 experiments with diphtheria were performed on the operated animals.

The results of these experiments showed that the cats with very severe tetanus and diptheria died at the same time as the control animals, with no sign of restoration of the contractions of the diaphragm on the side of the preliminary hemisection of the spinal cord. However, the fact that in these experiments division of the phrenic nerve on the opposite side led to the appearance of the crossed phrenic phenomenon proved that the crossed connections were intact after the action of these toxins. Following preliminary transection of the spinal cord the picture of the lesion caused in the cats by botulism toxin differed significantly from that observed in the controls. The operated animals survived until the third-fifth day after injection of the lethal dose of toxin, whereas the controls died on the second day.

In general clinical observations and during mechanographic recording of the contractions of the diaphragm in cats it has been found that in the early stages of botulism the crossed phrenic phenomenon can be produced only by the "classical" technique—after division of the opposite phrenic nerve. At the stage of marked pareses of the skeletal

muscles, as in the experiments described above, we observed contractions of both cupolas of the diaphragm, but during the development of generalized paralyses (Fig. 2) the contractions of the diaphragm on the intact side disappeared completely, while on the side of the hemisection of the spinal cord the diaphragm continued to contract for a considerable time (up to 2 days). Because of this mechanism of compensation of respiration, the operated animals survived longer after the second operation than did the controls. Hence, the results of the experiments with generalized botulism showed that a temporary delay of the action of the toxin on one nucleus of the phrenic nerve caused by preliminary hemisection of the spinal cord enabled this nucleus to function for a long time even though the activity of the other divisions of the motor nerve supply to the skeletal muscles was completely excluded. This showed that in generalized botulism the cause of death is not paralysis of the respiratory center or conducting pathways, but a marked depression of the activity of the motor innervation of the respiratory muscles.

Analysis of the respiratory disturbances in local and generalized forms of bacterial neurotoxicoses shows that in botulism the mechanisms of the paralytic action of the toxin on the respiratory muscles are apparently the same as on other skeletal muscles [8]. The principles governing the development of the respiratory disorders in diptheria and tetanus differ essentially from those described in botulism, and probably affect several links of the nervous apparatus of respiration. Further investigations are required to shed light on this problem.

SUMMARY

Using the crossed phrenic phenomenon as a test, the authors demonstrated that respiratory paralysis in botulism was caused by depression of motor innervation function of respriatory muscles and not by the exclusion activity of the respriatory center.

Disturbances of respiration in tetanus and diptheria are due to another, more complicated mechanism.

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