

THE MECHANISM OF THE DISORDERS OF RESPIRATION IN TOXIC FORMS OF DIPHTHERIA

COMMUNICATION I. THE EFFECT OF DIPHTHERIA TOXIN ON THE FUNCTIONAL STATE OF THE RESPIRATORY CENTER IN GUINEA PIGS

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As clinical observations show [7, 8, 12], in toxic forms of diphtheria respiratory disorders play a leading part. Paralysis of the respiratory muscles — the intercostals and diaphragm [6] — are dangerous to life and are often complicated by pneumonia. In laryngeal diphtheria there is often spasm of the muscles of the larynx. The mechanism of spasm is connected with the increased excitation of the peripheral receptors on the one hand, and on the other with factors of a conditioned reflex and psychogenic order [3, 12, 14].

Very few experimental investigations have been devoted to the study of the respiratory disorders in diphtheria. N. M. Porubinskaya [9, 10] put forward the suggestion of inoculation of rabbits with a diphtheria culture through a puncture of the larynx as an experimental model of laryngeal diphtheria. Her morphological research supports the opinion of clinicians that the cause of stenosis and asphyxia in laryngeal diphtheria is a neuroreflex spasm of the muscles of the larynx.

Enriquez and Hallion [16] point out that disturbances of respiration under the influence of diphtheria toxin are associated with a fall in the blood pressure, which is the direct cause of death of the animals.

V. O. Krasnov [5] emphasizes the importance of disorders of respiration in the picture of experimental toxic diphtheria in cats and dogs. The author associates a lesion of the inspiratory center with paralysis of the endings of the phrenic nerve. At the same time, this worker points out that the excitation of the respiratory center gradually and progressively falls in toxic conditions, and death of the animals in experimental diphtheria occurs from respiratory paralysis.

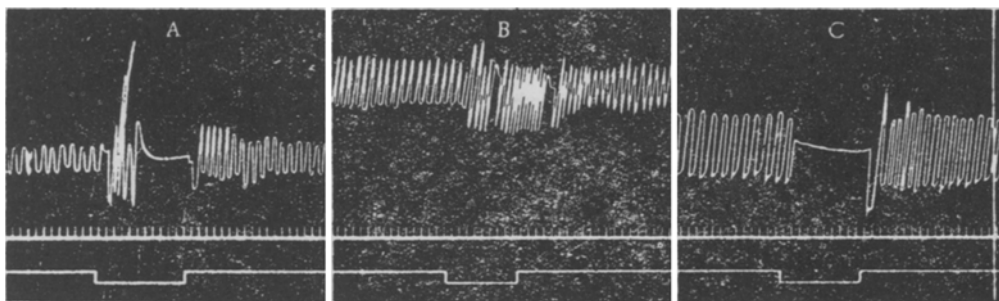
Recently V. N. Abrosimov [1, 2] has studied the changes in the respiratory movements during toxic diphtheria in rabbits and cats. He used an induction current to stimulate the central part of the vagus and also the sciatic nerves, and found that in cases of poisoning with diphtheria toxin the threshold of stimulation rises; the author associates this with reduced excitation of the respiratory center.

The aim of the present investigation is to study the excitation and the physiological lability of the respiratory center during the action of diphtheria toxin on guinea pigs.

Since an important role in the reflex regulation of respiration is played by the vagus nerve, we employed stimulation of its central segment to judge the functional state of the respiratory center.

EXPERIMENTAL METHOD

Altogether 39 experiments were carried out on 26 guinea pigs. The experiments were performed without anesthesia, or under light urethane anesthesia. The respiration was recorded by a Marey's capsule connected to



Changes in respiration in guinea pigs under the influence of diphtheria toxin.

A - Effect of stimuli at a frequency of 80 cps before injection of toxin; B - the same 27 minutes after injection of 0.5 MLD of diphtheria toxin; C - the same 19 minutes after a second injection of toxin (20 MLD). Significance of the curves (from above downward): respiration (inspiration - downwards), time marker (1 second), stimulus marker.

a cannula inserted into the trachea. The right vagus nerve was divided and its central end stimulated by means of an electric current. In some experiments both vagus nerves were divided. The source of stimulation was a tube generator of rectangular stimuli in which the current voltage could be changed between limits of 0 and 60 v, and the frequency of the impulses from 1 to 1400 cps. The state of excitation of the respiratory center was judged by determination of the threshold of stimulation of the afferent fibers of the vagus nerve at a frequency of 10 cps before obtaining minimal changes in respiration. Subsequent stimulation was carried out at a current voltage three times above the threshold level. The physiological lability of the respiratory center was judged by changes in the character of respiration in response to stimulation of the central end of the vagus nerve by current impulses of varying frequency. Diphtheria toxin was injected intraperitoneally, as a rule in a dose of 1 MLD, but in individual experiments in doses of 0.1 to 100 MLD. These indexes of the physiological activity of the respiratory center were determined repeatedly before the injection of toxin and at various intervals of time after its injection.

EXPERIMENTAL RESULTS

The threshold of stimulation of the central end of the vagus nerve before the first minimal changes in respiration (usually a quickening and deepening) varied insignificantly, and was on the average 0.9 v in the experiments without anesthesia and 1 v in the experiments on animals feebly anesthetized with urethane.

The use of different frequencies of stimulation resulted in the discovery of the following general relationship. At low frequencies (10-20 cps) the respiration of the guinea pigs was quickened and deepened, and with increase of the frequency (40-60 cps) a biphasic reaction was usually observed: the rate of respiration increased and then began to fall. On increasing the frequency of stimulation to 60-80 cps, the respiration rate fell. Finally, at even higher frequencies (80, or even 100-120 cps) respiration ceased. Cessation of respiration developed as a rule at the beginning or in the middle of the phase of inspiration, and lasted throughout the whole period of stimulation (usually 10 seconds). Sometimes at high frequencies (140 or 160 cps) respiration was restored very soon after the end of the period of stimulation.

During the action of diphtheria toxin the threshold of stimulation of the central end of the vagus nerve is usually raised. For example, in one of the experiments the initial threshold of stimulation at a frequency of 10 cps was 1 v, and 30 minutes after the intraperitoneal injection of only 0.1 MLD of toxin it was 2.25 v. If the diphtheria toxin (1 MLD subcutaneously) was injected earlier, many hours before the experiment, then for the first 24 hours after injection the threshold of stimulation of the central end of the vagus nerve corresponded roughly to the threshold in normal guinea pigs, or it was slightly above the normal value. At the same time, at the end of the second day after injection of toxin the threshold was sharply increased, sometimes reaching 9 v. This demonstrates a fall in the excitation of the respiratory center during the action of diphtheria toxin.

The use of different frequencies of stimulation showed that after the action of toxin the limit of appearance of biphasic reactions, slowing of the rhythm and cessation of respiration is displaced towards the higher frequencies (see Figure, A, B). In toxic conditions, during the action of high frequencies of stimulation it is

The Influence of Diphtheria Toxin on the Physiological Lability of the Respiratory Center

Changes in respiration	Frequency (in cps)	
	before action of toxin	after action of toxin
Transition from quickening to slowing	40-60	80-140
Slowing	60-80	100-160
Cessation	80-120	120-180

easier to obtain quickening than slowing of the respiratory rhythm.

The changes in the physiological condition of the respiratory center in this direction are quite regular and are duplicated in all the experiments without exception. At frequencies which before infection of toxin caused a slowing of the respiratory rhythm, after injection a quickening and strengthening of respiration was observed. The figures given in the right hand column of the table show the changes in respiration observed from 15-30 minutes to 1 hour and more after the intraperitoneal injection of diphtheria toxin.

After the action of large doses of diphtheria toxin – from 4 to 20 and 100 MLD, and also in some cases from 1½ to 2 hours and more after the ordinary dose used (1 MLD)—another type of reaction could be observed. A shift in the optimal conditions for activation of respiration and for inhibition respectively took place in the direction of lower frequencies (see Figure, C).

The vagus nerve is known to play an essential part in the regulation of breathing of the animal (Hering-Breuer reflex). In order to judge the functional state of the respiratory center many research workers [4, 11, 13, 15, 17] have employed stimulation of the central end of this nerve. The investigations have been carried out mainly on rabbits, cats and dogs. We succeeded in observing the above-mentioned characteristic changes in respiration in guinea pigs by the action of stimuli of different frequencies, which are distinguished from the changes in respiration under similar conditions in other species of animals.

The fall in excitation of the respiratory center which we observed in guinea pigs under the influence of diphtheria toxin is in agreement with the reports in the literature [1, 2, 5] on the fall in the excitation of the respiratory center of rabbits and cats under the same conditions. Our experiments carried out on rabbits also confirm these findings.

Displacement of the zone of optimum frequency in the direction of the more powerful and frequent stimuli is regarded by physiologists, studying the physiological lability of the cerebrospinal centers, as an index of increase in the physiological lability of the nerve centers. By analogy with this view it may be postulated that in our experiments the first phase of the changes in the functional condition of the respiratory center under the influence of diphtheria toxin is characterized by an increase in physiological lability. In the second stage, by the action of large doses of toxin, a change takes place in the optimum for stimulation and subsequent inhibition of respiration in the direction of the lower frequencies, and this evidently is an indication of a reduction in the physiological lability of the respiratory center.

The biphasic changes in physiological lability of the respiratory center which we observed after the injection of diphtheria toxin are peculiar to the action of diphtheria toxin, since in control experiments with Martin's broth and typhoid toxin results close to those described above were not obtained.

SUMMARY

The effect of diphtheria toxin on the functional condition of the respiratory center was studied in guinea pigs. It was demonstrated that diphtheritic intoxication is associated with decreased excitability of the respiratory center and with vast changes in its physiological lability. The first phase of intoxication is characterized by a constant increase in the physiological lability of the respiratory center, while the second – by its decrease.

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