EFFECT OF MORPHINE ON THE ELECTRICAL ACTIVITY OF INDIVIDUAL BULBAR RESPIRATORY NEURONS

(UDC 612.828 : 612.014.423]-06 : 615.783.1 + 615.783.1-092 : [612.828 : 612.014.423]

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Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 59, No. 4,
pp. 53-57, April, 1965
Original article submitted February 11, 1964

The action of morphine on the respiratory center has been studied by means of local electrostimulation and transection of the brain stem [1, 5, 10], which did not make it possible to obtain direct data characterizing the changes in the activity of neurons participating in the generation of the respiratory rhythm. Therefore, we undertook to study the effect of morphine on the electrical activity of individual respiratory neurons of the medulla oblongata, since according to current concepts the activity of precisely these neurons provides the alternation of the phases of inspiration and expiration [4, 12].

In addition, it was proposed to compare the changes in the discharges of the respiratory neurons occurring after the injection of morphine with the change of the constant spontaneous discharge of other neurons of the reticular formation of the medulla oblongata.

METHOD

The experiments were set up on 60 cats decerebrated between the superior and inferior colliculi. Under ether, after ligation of the common carotid arteries, we performed a resection of the occipital bone and removal of the lower parts of the cerebellum, which provided access to the respiratory zone of the medulla oblongata. After the administration of ether, $1^1/_2$-2 h passed before starting the experiment. During the experiments the animals breathed independently.

The extracellular tapping of the action potentials of the respiratory neurons was done with 30 μ nichrome electrodes in a glass insulation. The electrodes were inserted into the medulla oblongata by a micromanipulator in a vertical direction in the zone where the probability of "hitting" the respiratory neurons was greatest (rostrolateral of the obex [3, 8]).

The action potentials were amplified by an alternating-current amplifier and recorded on photographic film by a magnetoelectric oscillograph. We simultaneously recorded the action potentials of the diaphragm, which were tapped by needle electrodes. Furthermore, respiration was recorded on a kymograph, using a capsule connected with the interpleural space.

Control of the localization of the microelectrode was done by the method of microelectrolysis.

The morphine was injected intravenously in a dose of 2 mg/kg. It was possible to trace the changes of the activity of individual neurons after the injection of morphine only on 18 neurons (6 inspiratory, 4 expiratory, 8 with a constant spontaneous discharge).

RESULTS

As the histological control showed, upon inserting the tip of the microelectrode to a depth from 1.5 to 4 mm, tapping of the action potentials of the respiratory neurons in all experiments was done from the parvicellular reticular nucleus.

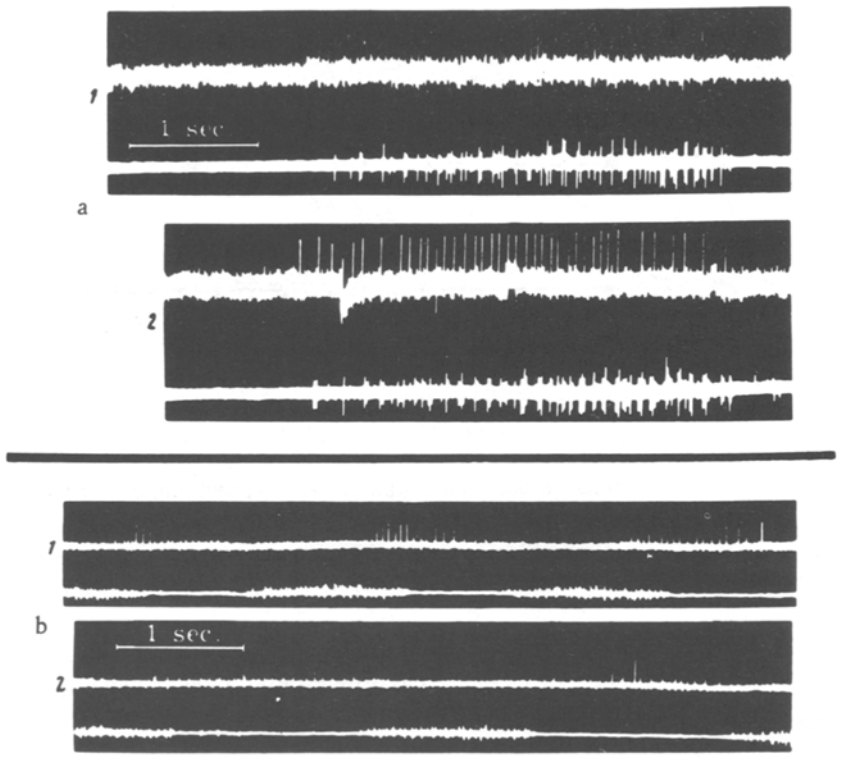

Fig. 1. Activity of individual inspiratory (a) and expiratory (b) neurons before (1) and after (2) injection of 2 mg/kg of morphine. Upper recording—action potentials of neurons; lower recording—action potentials of diaphragm.

The activity of the respiratory neurons in the norm was demonstrated by volleys of impulses coinciding in time with the phase of inspiration or expiration. Irregularity is characteristic for discharges of respiratory neurons, i.e., the absence of a regular distribution of frequency during the course of the discharge and an appreciable inconstancy of the interpeak intervals. The average frequency of the impulses in the volley was constant for each individual neurons, but from neuron to neuron it varied within wide limits (from 9 to 38 impulses/sec).

Morphine in a dose of 2 mg/kg caused a 20-40% decrease of the respiratory rate. There was a shortening of the inspiratory phase with respect to the duration of the respiratory cycle (by 10% on the average). The characteristics of the discharges of the inspiratory and expiratory neurons changed to a dissimilar degree.

The discharges of the inspiratory neurons became shorter and included a fewer number of peaks (Fig. 1, a). The rate of onset of these changes and their degree of evidence were different for individual neurons. But, as a rule by the 30th minute after the injection of morphine the discharge was shortened by 5-15% (Fig. 2, A), but the number of peaks in the discharge dropped 15-30% (Fig. 2, B). As a consequence of the fact that the number of peaks dropped to a greater degree than the duration of the discharge, the average frequency of the impulses in the discharge was reduced (Fig. 3). The absolute duration of the inspiratory phase, determined by the time of diaphragmatic contraction, after the injection of morphine did not change, or even increased. In this case the discharges of the inspiratory neurons, the duration of which dropped, occupied a smaller portion of the inspiratory phase than in the norm.

The duration of the expiratory discharges increased in conformity with lengthening of the expiratory phase. The number of impulses in the discharge also increased (see Fig. 1, B and 2, A, B), but their average frequency dropped.

An analysis of the average indexes of the activity of individual neurons shows that the discharges and the number of impulses in the discharges of the expiratory and inspiratory neurons under the effect of morphine varied in opposite directions (see Fig. 2). However, the average frequency of the discharge dropped almost to the same extent for neurons of both groups: by 20-30% for inspiratory and by 15-40% for expiratory neurons (see Fig. 3).

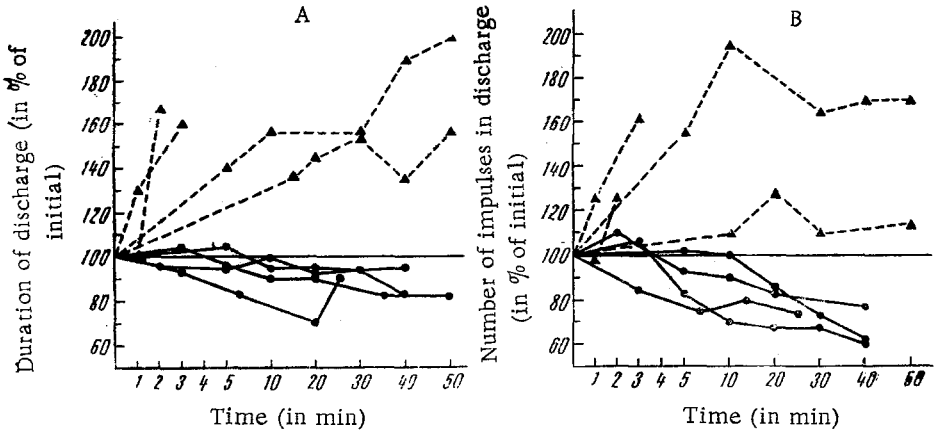

Fig. 2. Change of the discharge duration of the neuron (A) and number of impulses in the discharge (B) after the injection of 2 mg/kg of morphine. Along axis of abscissa is the time after injection of morphine; ● ——— ● inspiratory neurons; Δ ——— Δ expiratory neurons.

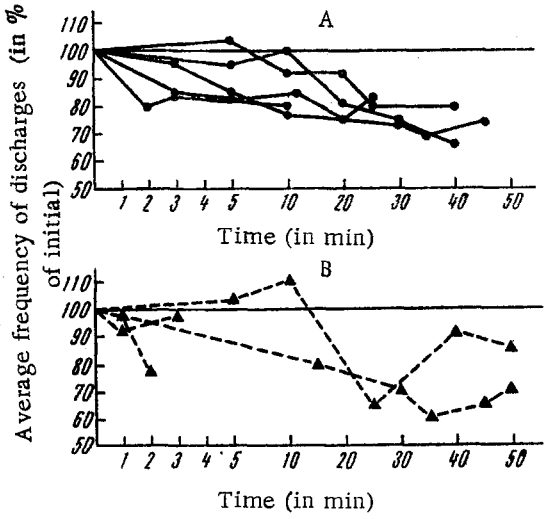

Fig. 3. Change of the average frequency of the discharge of inspiratory (A) and expiratory (B) neurons after the injection of 2 mg/kg of morphine. On all figures the time after the injection of morphine is plotted along the abscissa.

The changes of the discharges of the respiratory neurons differed from those which ensued under the effect of morphine, i.e., of the reticular neurons of the medulla oblongata which produced a constant spontaneous discharge. In our experiments spontaneous discharges with an irregular rhythm and frequency of 0.5-30 impulses/sec were derived from various reticular neurons. In two cases, as a consequence of the action of morphine, there was a twofold increase of frequency of the discharge, in three cases a 15-30% decrease of frequency, and in three cases the spontaneous activity did not change. The direction of the changes did not depend on the initial frequency of the discharge. Thus, the spontaneous activity of the reticular neurons, which is not associated with the respiratory phases, changed differently under the effect of morphine.

It is known that the spontaneous activity of neurons of the reticular formation is supported by impulses arriving at it from various afferent systems [8, 11]. Moreover, these neurons are subjected to the inhibitory effect from the lower divisions of the central nervous system. Upon injection of morphine the spontaneous activity of the individual reticular neuron can change as a consequence of a change of the relationships of the inhibitory and excitatory effects converging on a given neuron.

This indirect action of morphine cannot cause similar shifts in the activity of different reticular neurons since even with a close arrangement they do not have common sources of inhibitory and excitatory stimuli [2].

Other relationships are composed in the respiratory neurons, which are combined into a single functional system reacting as a whole to afferent effects. In each of the groupings of respiratory neurons—inspiratory and expiratory—the activity of individual nerve cells is changed in the same way by morphine.

It follows from our experiments that the functioning of the inspiratory population is disrupted under the effect of morphine more significantly than the expiratory. The discharge of inspiratory neurons becomes shorter and more frequent and occupies a smaller segment of the inspiratory phase than in the norm. This can be the result of disruption of the synchroneity in the work of the inspiratory population, i.e., such a state where in individual neurons the

discharges begin later and end sooner than in the bulk of the cells. Such a "mismatch" with the expiratory phase was not detected in the expiratory neurons, their discharge was lengthened and consisted of a greater number of peaks.

It is known that the inspiratory and expiratory groupings of neurons are in reciprocal relations [4, 12]. Upon a decrease of the activity of the inspiratory grouping there is a weakening of its inhibitory effect on the expiratory grouping, the discharges of neurons of which become longer, and the frequency of occurrences of impulses increases. Such facilitation of the expiratory activity is observed, for example, upon inhalation of pure oxygen [3]. The action of morphine cannot be reduced to unilateral suppression of the inspiratory groupings since the preparation equally reduces the frequency of discharges of both the inspiratory and the expiratory neurons. Consequently, morphine suppresses respiratory neurons of both groupings, but the inspiratory to a greater degree.

Weakening of the activity of the respiratory neurons can occur either as a consequence of a decrease of the afferent current, or as a result of the direct suppressing action of morphine on these cells. On the basis of our experiments indirect data were obtained in behalf of the direct action of morphine. First, the disorders of the activity of the respiratory neurons upon limitation of the afferent current differed from those changes which ensued after the injection of morphine. For example, during hyperventilation when the impulses from the receptors reacting to hypoxia and the increase of the CO_2 level decreased, there was a shortening and a decrease in frequency of both the inspiratory and the expiratory discharges [6]. Second, if we assume that morphine acts on the respiratory center only by limiting the afferent inflow, then it is difficult to explain why it inhibits to a different degree the inspiratory and expiratory neurons. The opinion on the direct action of morphine on the system of respiratory neurons is in accord with the data of other authors who have established that morphine weakens the sensitivity of the respiratory center to direct electrical stimulation [1, 10] and to an increase of the partial pressure of CO_2 [7].

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