EFFECT OF FENTANYL ON SINGLE UNIT ACTIVITY IN THE BULBAR RESPIRATORY CENTER

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UDC 615.212.3:547.822.3].015.4:612.282

Experiments on decerebrate cats showed that fentanyl, in a dose of 10 μg/kg or more, inhibits neurons of the bulbar respiratory center, with a resulting decrease in the mean firing rate, a change in the number of spikes in the discharge and its duration, and disturbance of the temporal distribution of spikes in the discharge. The degree of inhibition of the inspiratory neurons depends on the initial firing rate. Inhibition of activity of the expiratory neurons is more pronounced.

KEY WORDS: fentanyl; respiratory center; respiratory neurons.

There is little information in the literature on the effect of fentanyl on external and tissue respiration [5, 6] and virtually no information on its action on unit activity in the respiratory center.

The present investigation was carried out to study this problem.

EXPERIMENTAL

Fifteen cats were used. The preparatory operation (decerebration and removal of the cerebellum) was carried out under deep ether anesthesia. At least 2 h elapsed between discontinuing the ether and starting the experiment. During the experiment the animals breathed spontaneously.

Activity of the respiratory neurons was recorded extracellularly by electrodes with a tip 20-40 μ in diameter. The microelectrode was inserted into the brain in an area rostro-laterally to the obex, where the probability of finding respiratory neurons is highest [9, 11].

Bioelectrical activity of the diaphragm was recorded simultaneously with bipolar needle electrodes. Action potentials of the respiratory neurons and potentials of the diaphragm were suitably amplified (UBP1-01 amplifier) and recorded on moving photographic film from the screen of a dual-beam oscilloscope (S1-18).

Fentanyl citrate was injected intravenously in split doses up to a total of between 10 and 100 μg/kg. The injections were given slowly over a period of 1-2 min.

RESULTS AND DISCUSSION

The spontaneous activity of 12 inspiratory and 3 expiratory neurons was recorded. To assess the single unit activity and its changes under the influence of fentanyl, the following indices of periodic discharges were used: the mean firing rate, the number of spikes per discharge, the duration of discharge, and the temporal distribution of spikes in the discharge.

Fentanyl led to a mean decrease of 30-40% in the respiration rate and the relative duration of inspiration was reduced. The duration of expiration in all cases was increased by 75% after a dose of 10 mg/kg and it increased progressively with an increase in the dose up to 50-70 μg/kg.

Department of Pharmacology, I. P. Pavlov First Leningrad Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR S. V. Anishkov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 78, No. 12, pp. 35-38, December, 1974. Original article submitted February 11, 1974.

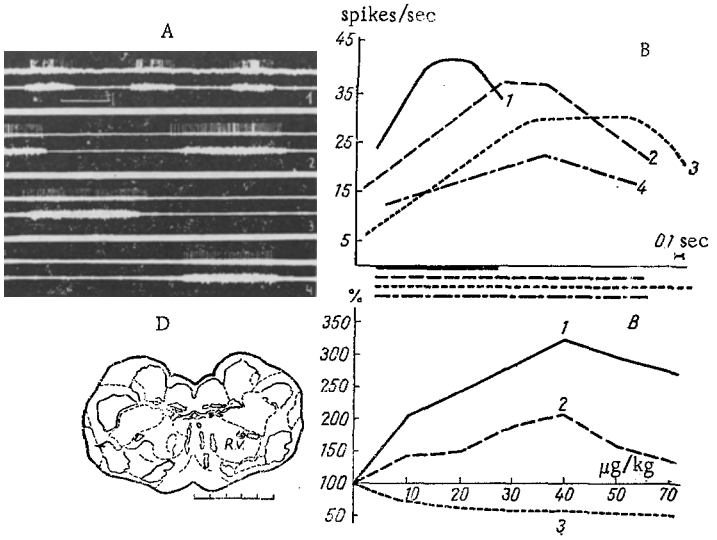

Fig. 1. Effect of fentanyl on activity of group 1 inspiratory neurons. A) Discharges of inspiratory neuron (top beam) and of diaphragm (bottom beam); 1) normal; 2, 3, 4) after administration of fentanyl in doses of 10, 40, and 70 μg/kg, respectively. Calibration in this and all subsequent records: time, 1 sec; amplitude, 100 μV. B) Frequency characteristic curves of the same neuron; 1) normal; 2, 3, 4) after injection of fentanyl in doses of 10, 40, and 70 μg/kg, respectively. Abscissa, time (in sec); ordinate, firing rate. Lines under abscissa show duration of discharges of diaphragm. C) Aggregated curves of discharge duration (1), number of spikes per discharge (2), and mean frequency (3) of inspiratory neurons under the influence of fentanyl. Abscissa, dose of fentanyl (in μg/kg); ordinate, change in corresponding parameters (in % of initial level). D) diagram of frontal section through brain stem showing location of tip of recording electrode.

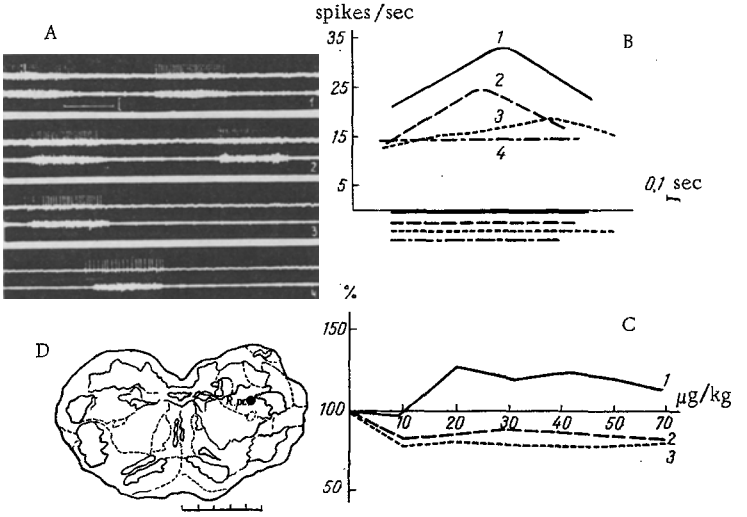

Fig. 2. Effect of fentanyl on activity of group 2 inspiratory neurons. Legend as in Fig. 1.

Three groups of inspiratory neurons were distinguished on the basis of the degree and direction of the changes in the principle indices under the influence of fentanyl.

In the neurons of group 1 (four units), with a high mean spontaneous firing rate (Fig. 1), an increase in the duration of the discharge was observed immediately after injection of fentanyl in a dose of 10 μg/kg, to reach a maximum with doses of 40-50 μg/kg (Fig. 1C). The number of spikes per discharge also was

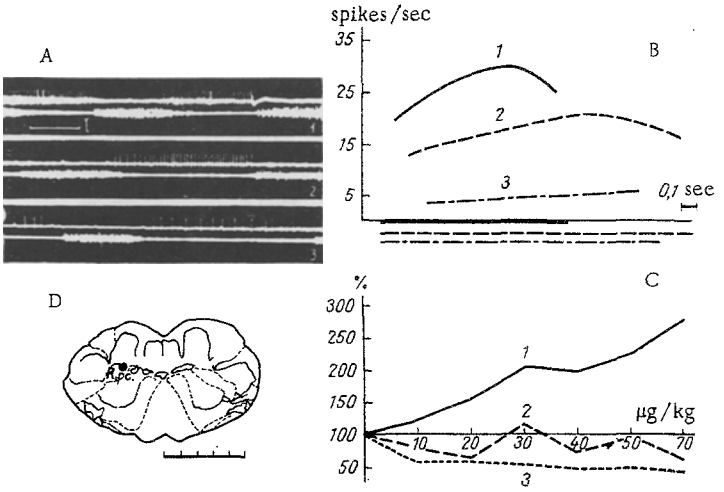

Fig. 3. Effect of fentanyl on activity of expiratory neurons. In A and B: 1) normal; 2, 3) after injection of fentanyl in doses of 30 and 70 μg/kg, respectively. Remainder of legend as in Fig. 1.

increased, although the mean firing rate fell gradually on the average by 45% of its initial level. Analysis of the changes in the frequency characteristic curve (Fig. 1B) showed high resistance of the discharge structure to the action of fentanyl. Only after doses of 50-70 μg/kg was flattening of the characteristic curve observed. With small doses of fentanyl, earlier recruiting of neurons into the discharge took place, but with large doses this change was less marked (Fig. 1A).

In the neurons of group 2 (four units), with a lower mean spontaneous firing rate (from 16 to 24/sec), much greater inhibition of activity was observed under the influence of fentanyl. The duration of the discharges in this group increased on the average by 20-25% (Fig. 2C). The number of spikes in the discharge fell by 10-15%. The mean firing rate fell progressively. Flattening of the frequency characteristic curve was pronounced (Fig. 2B), and with doses of fentanyl of 50-70 μg/kg a discharge with constant frequency appeared; the beginning of the discharge was shifted into the phase of expiration (Fig. 2A).

In the neurons of group 3 (four units), with a low mean firing rate (from 13 to 17/sec), under the influence of fentanyl changes in the duration of the discharge and the number of spikes per discharge took place in two phases: an increase after the injection of small doses and a decrease after injection of large doses. The mean frequency fell in all experiments. There was a clear tendency toward flattening of the frequency characteristic curve followed by its inversion (with large doses of fentanyl).

Maximal changes in the principle indices of unit activity occurred 1-2 min after the injection of fentanyl, followed by partial recovery at the 10th minute of observation.

The duration of the discharge of the expiratory neurons was increased on the average by 100% by fentanyl in a dose of 30-40 μg/kg (Fig. 3C). The number of spikes did not change significantly. The mean frequency fell by 50% after a dose of 30-40 μg/kg. Starting with a dose of 30 μg/kg a tendency toward flattening of the frequency curve was observed, and with a dose of fentanyl of 70 μg/kg either inversion of the curve or a discharge with constant frequency was observed (Fig. 3B).

The results show that under the influence of fentanyl the activity of the inspiratory neurons was inhibited; the degree of inhibition depended on the original mean firing rate. This pattern of relationship was not observed with morphine [3, 4]. The difference may be explained by the unequal action of fentanyl on neurons located in the center and at the periphery of the respiratory nucleus [1, 2].

In the present experiments the changes taking place were not found to depend on the location of the discharge in the respiratory cycle, as is characteristic, for example, of pentobarbital [2, 3].

Like morphine [7], fentanyl disturbs the distribution of the discharge frequency in the volley, an invariant parameter. This effect of fentanyl is stronger than that of morphine, as shown by inversion of the frequency characteristic curve, a reflection of a severe disturbance of the self-excitation process.

Slowing of the respiration rate after doses of fentanyl too small to give any marked change in unit

activity, together with the increase in the discharge duration of neurons of both the "generator" groups, are evidence of the predominant action of fentanyl on the system of "intermediate" neurons of the pons [8, 10]. However, this hypothesis requires further confirmation.

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