EFFECT OF CHLORPROMAZINE ON RESPIRATION IN THE FROG

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Many authors [1,9,12,14] have reported a slowing of respiration, a fall of blood pressure, and a slowing of the heart rate after administration of chlorpromazine in observations on human subjects and experiments on warm-blooded animals.

Chlorpromazine has a dual effect on the different regions of the reticular formation of the brain stem. The action of chlorpromazine on the hypothalamus has been studied [22,26]. M. V. Serbinenko [15] has localized the site of action of chlorpromazine between the rostral border of the corpora quadragemina and the anterior border of the medulla. Chlorpromazine acts on the spinal cord in very large doses, in consequence of which the direct physiological effect of the drug has been denied by many researchers [16,20,21,25].

Among the extensive literature on this subject there is only one paper [17] dealing with the investigation of the effect of chlorpromazine on the isolated frog's heart. The localization of the action of chlorpromazine on the frog's nervous system is of considerable interest. It has been suggested that the reticular formation of the frog is more extensive and less specialized than in warm-blooded animals, and that it is of great structural and functional importance.

The effect of chlorpromazine on respiration was studied in frogs after transection of the brain stem at different levels.

EXPERIMENTAL METHOD

Experiments were conducted on autumn and winter specimens of the frog Rana temporaria. The movements of the mandibular membrane were recorded by a myographic method, and the frequency of respiration and the heart rate were determined. Visual observations were made on the changes in skin color, on the secretion of mucus, and on the animal's general motor reaction. Chlorpromazine was used in ampule form, diluted with isotonic NaCl to give a 0.025-0.1% solution. The drug was injected intravenously, under local anesthesia, in doses of between 0.01 and 0.2 mg per frog (i.e., 0.25-5 mg/kg body weight). The brain was divided $^1/_3$, $^1/_2$, and $^2/_3$ of the way along the optic lobes, and at the anterior border of the medulla.

EXPERIMENTAL RESULTS

Sixty experiments were conducted to investigate the effect of chlorpromazine on the frog's respiration, and control experiments were carried out in which isotonic NaCl solution was injected intravenously.

Experiments on intact frogs. Small doses of chlorpromazine (0.01-0.02 mg) stimulated pulmonary respiration (Fig. 1a). Average doses (0.04-0.08 mg), after a transient phase of stimulation, led to a slowing of respiration and to a decrease in its amplitude, the latter returning to its normal value sooner than the respiration rate (Fig. 1b). The test doses of chlorpromazine caused slowing of the heart rate, which returned to its normal value after 7-45 min. During repeated injection of chlorpromazine, the response to each successive injection was similar to the initial response, but rather more protracted. No obvious changes were seen in the amount of mucus secreted, and the animal's skin color became uniform.

Experiments on frogs after brain section. Brain section always led to depression or disappearance of pulmonary respiration and to the appearance of oscillations [11]. Injection of chlorpromazine (all doses) led to reappearance, or increase in the amplitude of pulmonary respiration (this effect was of brief duration when average doses were used)

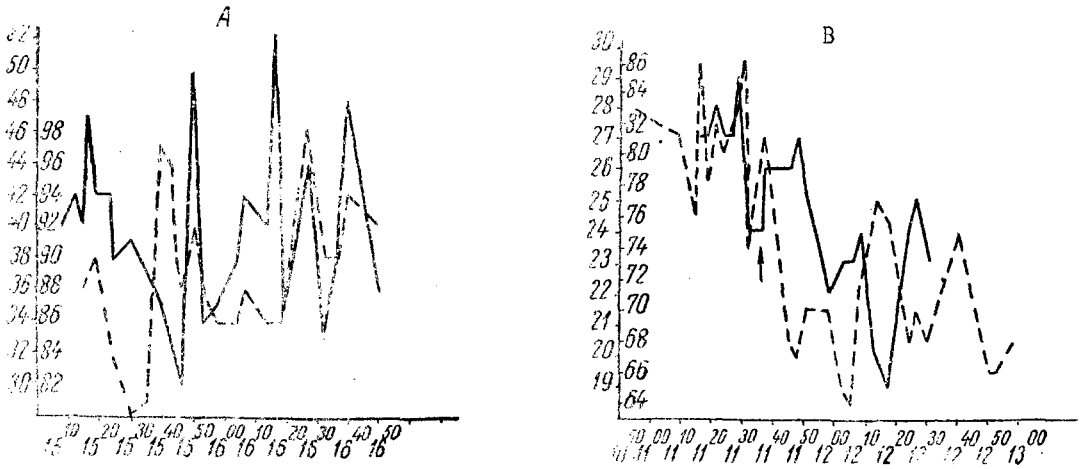

Fig. 1. Change in amplitude (continuous line) and frequency (broken line) or respiration of intact frog under influence of chlorpromazine. A) Small dose of chlorpromazine (0.015 mg); B) average dose (0.06 mg). The arrow indicates the moment of injection of chlorpromazine. Along the axis of abscissas – absolute time (intervals 10 min); along the axis of ordinates: on the left – amplitude (in mm), on the right – frequency of respiration per minute.

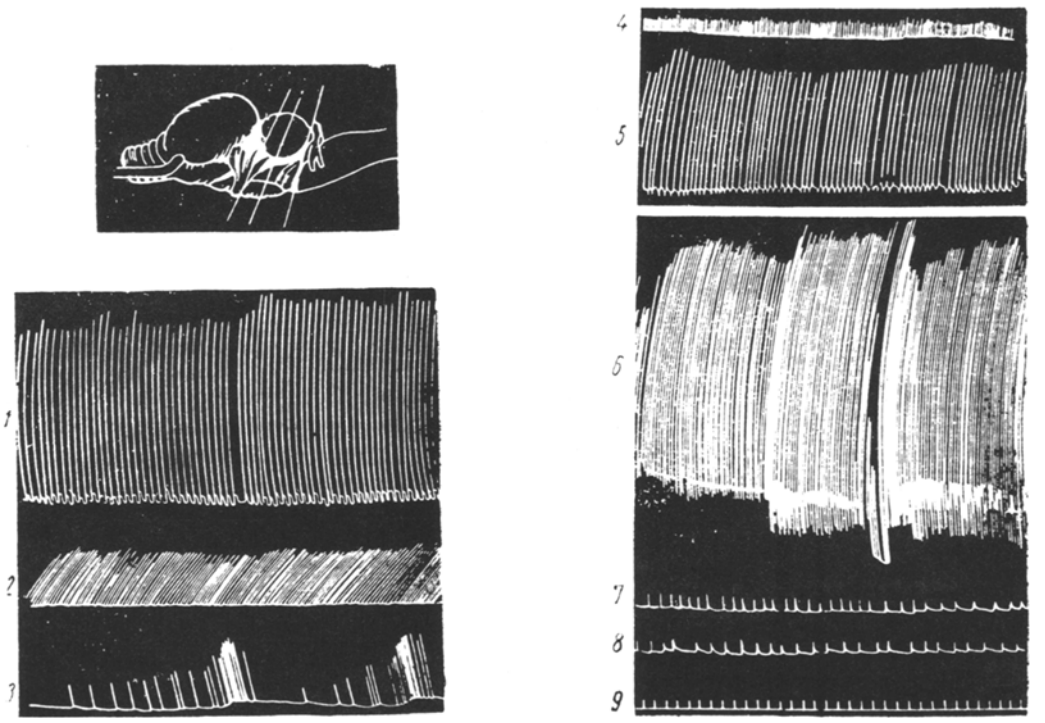

Fig. 2. Changes in respiration under the influence of chlorpromazine in frogs after section of the brain at different levels. Upper left) levels of brain section in frogs. 1) Initial (pulmonary) respiration (experiment No. 39); 2) oscillations appearing after brain section at the level of $^1/_3$ of the optic lobes; 3) periodic (pulmonary) respiration after injection of 0.06 mg chlorpromazine; 4) oscillatory respiration after section at the level of $^1/_2$ the optic lobes (experiment No. 40); 5) pulmonary respiration after injection of 0.06 mg chlorpromazine; 6) background (experiment No. 56); 7) pulmonary respiration after section anteriorly to the medulla; 8) the same, after injection of 0.06 mg chlorpromazine; 9) time marker (1 sec).

and almost completely suppressed the oscillations appearing after section (Fig. 2). The action of small doses of chlorpromazine (up to 0.03 mg) was accompanied by an increase in the respiration rate, as in the intact animals. Average doses, starting with 0.04 mg, slowed the respiration rate. After injection of large doses of chlorpromazine (0.1-0.2 mg) slow respiratory movements were observed to start when the head was raised or during generalized movement of the animal. In some experiments a dose of 0.2 mg caused death of the animal.

The excitatory action of small doses of chlorpromazine and the depressant action of large doses were observed by several workers in experiments on warm-blooded animals [19,23,24]. Periodic pulmonary respiration characteristically appeared [2,4] after injection of chlorpromazine, more frequently of average and large doses (Fig. 2,3). Chlorpromazine had no effect on the respiration of bulbar frogs; in these conditions it remained pulmonary in type and low in amplitude, and periodicity of respiration was absent (see Fig. 2). These observations support the claims of M. V. Serbinenko [15] that sensitivity to chlorpromazine falls from the cranial to the caudal end of the brain. I. G. Antonova [2] points out that for combined periodic respiration to take place the presence of the postero-inferior part of the mesencephalon and of the whole of the medulla is essential. According to Z. N. Ivanova [5], decapitation of a warm-blooded animal leads to the appearance of periodicity of respiration; the lower the level of brain section, the more marked the development of periodicity, until eventually Cheyne-Stokes breathing appears. In bulbar animals respiration does not show periodicity, although it is irregular in rhythm and amplitude.

Several authors explain the frog's periodic respiration by hypoxia [6,10,13,18], others attach the greatest importance to a reflex mechanism [4,7], while a third group implicate the functional state of the respiratory center [2,3,5]. Most investigators consider that periodic respiration may arise only in pathological states or when functional lability is lowered. An interesting attempt was made by D. G. Kvasov [8] to interpret this type of respiration not as a pathological phenomenon, but as a return to earlier stages of development, or at least as its reestablishment on a new basis, created by the changed conditions, of ontogenetically early structural relationships in the respiratory center.

In our opinion, the appearance of pulmonary respiration after administration of chlorpromazine to animals after brain section is associated with inhibition of the midbrain by the drug and the consequent liberation of the structures of the medulla from the restraining effect of the midbrain.

SUMMARY

A study was made of the effect produced by chlorpromazine on the respiration of intact frogs and of those with the brain divided at various levels. Medium and large chlorpromazine doses depress the respiration of intact animals. In frogs with divided brain chlorpromazine induces periodic respiration; in division above the medulla chlorpromazine does not influence the respiration, and periodic respiration is absent.

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