THE EFFECT OF CHLORPROMAZINE ON THE DEVELOPMENT OF THE FLEXOR DOMINANT

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A previous investigation [3] showed that during the action of adrenalin on the diencephalon of the frog the dominant of the flexor center of the spinal cord is intensified. Many reports in the literature show that adrenalin causes activation of the facilitating structure of the reticular formulation of the brain stem [25, 12, and others]. During recent years chlorpromazine has been widely used to exclude the function of these brain structures, in both experimental and clinical investigations [7, 8, 11].

The object of the present investigation was to study, using the method of local application of chlorpromazine to the region of the diencephalon and mesencephalon of the frog, the mechanism of action of this drug on the adrenergic structure of the rostral portion of the reticular formation of the brain stem and the role of these facilitating structures in the formation of the flexor dominant.

EXPERIMENTAL METHOD

Altogether 84 experiments were carried out on frogs (Rana ridibunda) after extirpation of the cerebral hemispheres. The distal portions of the central segments of the divided ipsilateral and contralateral peroneal nerves were placed on Dubois-Reymond electrodes, used to stimulate the nerves with pulses of current from a thyratron stimulator. Silver electrodes used to detect the potentials of the nerve were placed proximally at a distance of 2 cm from the stimulating electrodes on the ipsilateral peroneal nerve. The action potentials of the ipsilateral semitendinosus muscle were recorded by means of silver needle electrodes. The contractions of both semitendinosus muscles were recorded on a kymograph. The action potentials of the ipsilateral peroneal nerve and semitendinosus muscle were fed into an ac amplifier (transmission band from 1 to 3000 cps) and recorded on a type MPO-2 eight-loop oscillograph.

A study was made of the changes caused by the action of chlorpromazine on the flexor reflexes and the summation effects caused by stimulation of the ipsilateral and contralateral peroneal nerve after preliminary exposure to weak afferent stimuli causing the formation of a flexor dominant. Chlorpromazine was applied by means of filter paper (1 mm^2) soaked with solutions (0.1-3%) of the drug, to the section of the diencephalon and mesencephalon of the frog.

EXPERIMENTAL RESULTS

The results showed that chlorpromazine, in concentrations between 0.2 and 3%, had a depressant effect on the flexor reflexes and the summation properties of the centers. The intensity of these effects depended on the concentration of chlorpromazine and the duration of its action on the reticular structures of the brain stem. In addition, a significant role in this process was placed by the individual sensitivity of the animal to the action of chlorpromazine.

It is interesting to note that chlorpromazine produced a greater degree of depression in the flexor reflexes connected with the center in which the dominant had been produced and which, as a result of this, possessed the power of spatial summation.

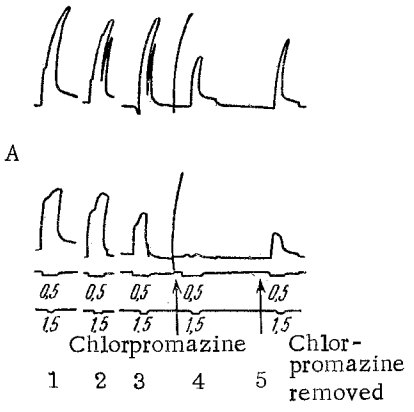


Fig. 1. Inhibition of spinal reflexes and flexor dominant by reaction of a 0.25% solution of chlorpromazine on the diencephalon and mesencephalon of the frog. A) Kymograms. Significance of curves (from top to bottom): reflex contractions of the contralateral semitendinosus muscle; reflex contractions of the ipsilateral semitendinosus muscle; marker of stimulation of ipsilateral peroneal nerve; marker of stimulation of contralateral peroneal nerve. 1, 2, 3, 4, 5—frame numbers; B) oscillograms. Significance of curves (from top to bottom): electrical potentials of ipsilateral peroneal nerve, electrical potentials of ipsilateral semitendinosus muscle, marker of stimulation of ipsilateral peroneal nerve, marker of stimulation of contralateral peroneal nerve, time marker (0.02 sec). The cuts 2, 4, and 5 of the oscillograms correspond to the frames of the recording of the myograms. Explanation in text.

B

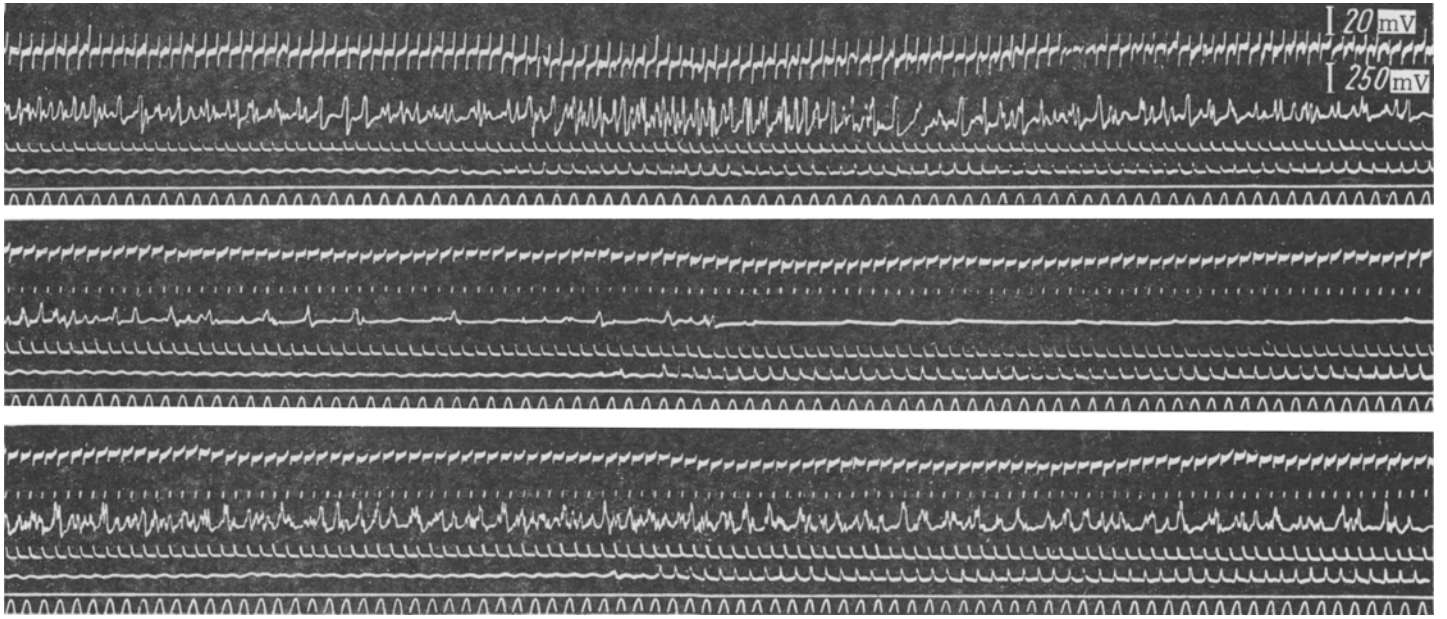
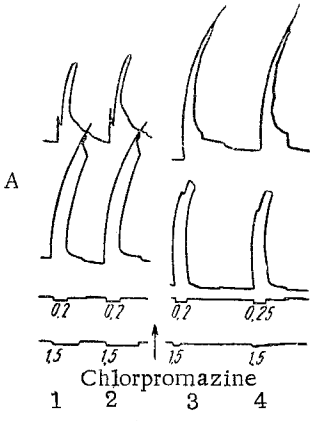
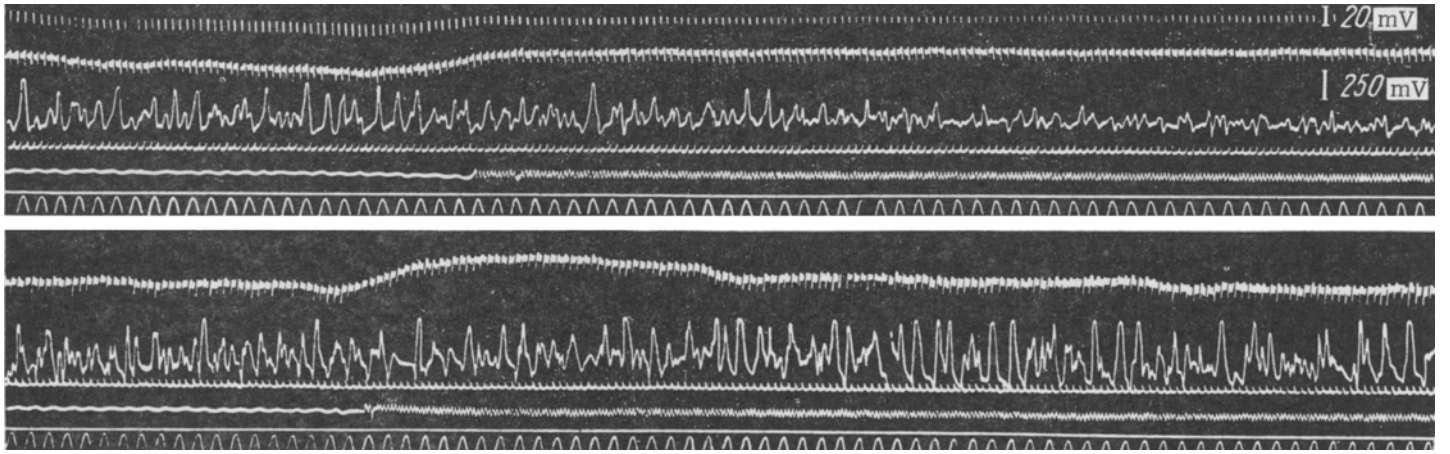


Fig. 2. Formation of a flexor dominant during the action of a weak (0.125%) solution of chlorpromazine on the diencephalon and mesencephalon. A) Kymograms. Significance of curves (from top to bottom): reflex contractions of contralateral semitendinosus muscle; reflex contractions of ipsilateral semitendinosus muscle; marker of stimulation of contralateral peroneal nerve; marker of stimulation of ipsilateral peroneal nerve. 1, 2, 3, 4—frame numbers; B) oscillograms. Legend as in Fig. 1B. Cuts 1 and 3 of the oscillograms correspond to the frames of recording of the myograms. Legend in text.





The myogram and oscillograms given in Fig. 1 may serve as an illustration. At the beginning of the experiment under the influence of subthreshold stimuli, a flexor dominant was produced and stimulation of the contralateral peroneal nerve against the background of stimulation of the ipsilateral peroneal nerve caused a marked increase in the amplitude of the flexor reflex (Fig. 1A, 2, 3) and an increase in the amplitude and frequency of the action potentials of the muscle (Fig. 1B, 2). Fifteen minutes after the beginning of the action of the 0.25% chlorpromazine solution on the diencephalon and mesencephalon of the frog, the flexor reflex from the ipsilateral side almost disappeared, and that from the contralateral side diminished (Fig. 1A, 4). During reflex stimulation action potentials of low amplitude developed in the muscle, and when stimulation was applied to the contralateral peroneal nerve these potentials disappeared (Fig. 1B), indicating inhibition of the flexor dominant. After removal of the chlorpromazine the flexor reflex was restored,and stimulation of the contralateral peroneal nerve no longer caused inhibition of the electrical potentials of the muscle (Fig. 1A, 5 and 1B, 5).

Different changes were observed during the action of weaker (0.1-0.2%) solutions of chlorpromazine (Fig. 2). At the beginning of the experiment stimulation of the contralateral peroneal nerve caused inhibition of the reflex contraction and a decrease in the potentials of the muscle (Fig. 2A, 1, 2 and 2B, 1).

During the action of a 0.125% solution of chlorpromazine the flexor reflexes remained intact or, as in some experiments, they actually became stronger. Stimulation of the contralateral peroneal nerve caused a marked increase in the amplitude of the reflex contraction and of the potentials of the muscle, instead of the inhibition observed at the beginning of the experiment (Fig. 2A, 3, 4 and 2B, 3), indicating development of summation properties in the centers and the formation of a flexor dominant. In those experiments in which the flexor dominant was formed previously, it was intensified under the influence of weak solutions of chlorpromazine. In some experiments biphasic changes were observed under the influence of chlorpromazine.

Hence, the results of these experiments showed that chlorpromazine solutions in concentrations greater than 0.2% depress the reflex function of the spinal cord, weaken the summation properties of the spinal centers, and inhibit a pre-existing flexor dominant. These facts, in conjunction with previous findings [3] suggesting an increase in the strength of a flexor dominant under the influence of adrenalin on the diencephalon of the frog, demonstrate the important role of the adrenergic structures of the reticular formation of the brain stem in the formation of the flexor dominant.

The experiments showed that under the influence of weak solutions of chlorpromazine, and also in the first phase of action of more concentrated solutions of the drug, the flexor dominant was intensified. In some experiments, in these circumstances an increase in the reflex contractions of the muscle was observed.

An intensification of the ascending activating influences of the reticular formation on the initial phase of action of chlorpromazine, as shown by a reaction of desynchronization of the cortical electrical activity, has been observed by several authors [4, 6, 10]. The same result has been noted [9] following administration of small doses of chlorpromazine to animals.

The facts described above may be explained by assuming that chlorpromazine has a biphasic action on the neural structures, causing the development of parabiotic inhibition in them. However, the first phase of action of chlorpromazine is ill-defined and is clearly manifested only under the influence of solutions of low concentrations of chlorpromazine. Solutions of higher concentrations of chlorpromazine rapidly lead to inhibition of the activity of the adrenergic-facilitating structures of the reticular formation of the brain stem and, as a result of this, as the present experiment showed, to a loss of the reflex excitability of the spinal cord and to disappearance of the summation properties of the centers. In these circumstances the flexor dominant was inhibited.

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