ON THE MECHANISM OF ACTION OF ANDAXIN IN EXPERIMENTAL TETANUS

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Andaxin (meprobamate) is presently used in the clinic as a tranquilizer and antispasmodic, particularly in the treatment of tetanus [5, 7, 9]. However, the mechanism of its action in this disease has been inadequately studied.

Results of an experimental study of this problem are presented below.

METHOD

The investigation was carried out on 17 mature rabbits with electrodes implanted in the brain. During the experiments we observed the changes in electrical activity of the optic and motor regions of the cerebral cortex, mesencephalic reticular formation, muscles of the hind legs, EKG, and respiration which occurred after injection of andaxin in animals with local tetanus of the left hind extremity that were not anesthesized.

To determine the functional shifts of individual structures of the brain that occurred under the effect of andaxin, we observed the changes in the thresholds of sound stimulation and stimulation of the mesencephalic reticular formation that had evoked an "activation" reaction in the cortical electroencephalogram (EEG) and enhancement of electrical activity of muscles affected by tetanus. The procedure for these experiments was described in detail in previous works [2].

Andaxin in a powder was dissolved with water and introduced into the stomach by means of a probe. Tetanic intoxication was induced by an injection of one minimum lethal dose of tetanus toxin into the left gastrocnemius muscle.

EXPERIMENTAL RESULTS

Andaxin in a dose of 250-400 mg/kg caused changes in the EEG of the rabbits 50-60 min after administration. The changes included the manifestation of high voltage potentials with a frequency of 12-16 vibrations per sec in all cortical leads to the EEG. The paroxysms of spindle-shaped volleys of impulses in the motor regions of the cerebral cortex became more frequent. The spontaneous electrical activity of the muscles affected by tetanus declined 1-1.5 h after administration of the drug (Fig. 1C, D). The described changes of the EEG and electromyogram (EMG) lasted 3-4 h and more. In the initial stage of the effect of andaxin, while still against a background of unchanged spontaneous electrical activity of muscles affected by tetanus, the threshold stimulation of the mesencephalic reticular formation by rhythmic electrical impulses (150 cps, 1 msec, 1-2 V) which before its administration had enhanced this activity, ceased to induce this effect. The threshold of this reaction increased by 0.5-2 V after administering andaxin and was restored only after 3-4 h.

At the same time the "activation" reaction in the cortical EEG caused by the same stimulation was retained at its previous threshold values (Fig. 2A, B). Only in certain rabbits were the ascending effects of the reticular formation also mitigated by andaxin.

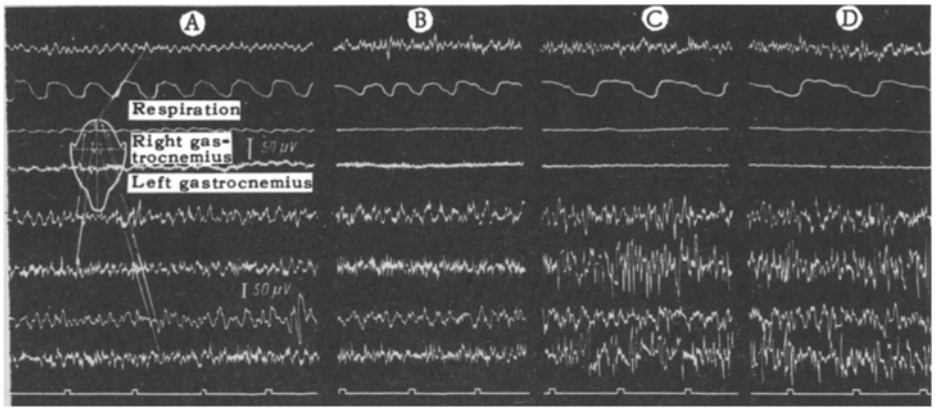

Fig. 1. Changes of the EMG, EEG, and respiration of a rabbit with local tetanus of the left hind leg under the effect of andaxin. Significance of the curves (top down): EEG of the mesencephalic reticular formation, respiration, EMG of the right and left gastrocnemius muscles, EEG of the right occipital, right motor, left occipital, and right motor regions of the cerebral cortex, time marker (1 sec). A) Before administration of andaxin; B) 30 min later; C) 50 min later; D) 3 h 45 min after oral administration of the drug in a dose of 325 mg/kg.

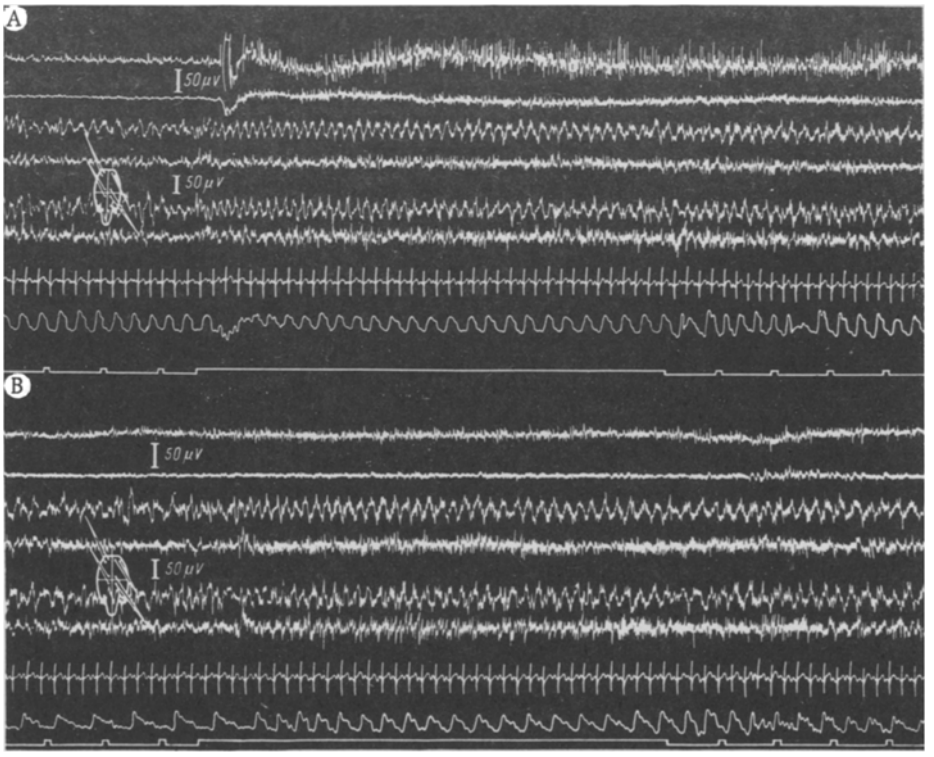

Fig. 2. Changes in the EMG, EEG, EKG, and respiration upon stimulation of the recticular formation of the mesencephalon in a rabbit with local tetanus of the left hind leg before (uppper picture) and after (lower picture) peroral administration of andazin in a dose of 310 mg/kg. The meaning of the curves (top down): EMG of the left and right gastrocnemius muscles, EEG of the right occipital, right motor, left occipital, and left motor regions of the cerebral cortex, EKG, respiration, time marker (1 sec). The rise in the time marker curve corresponds to the moment of stimulating the reticular formation.

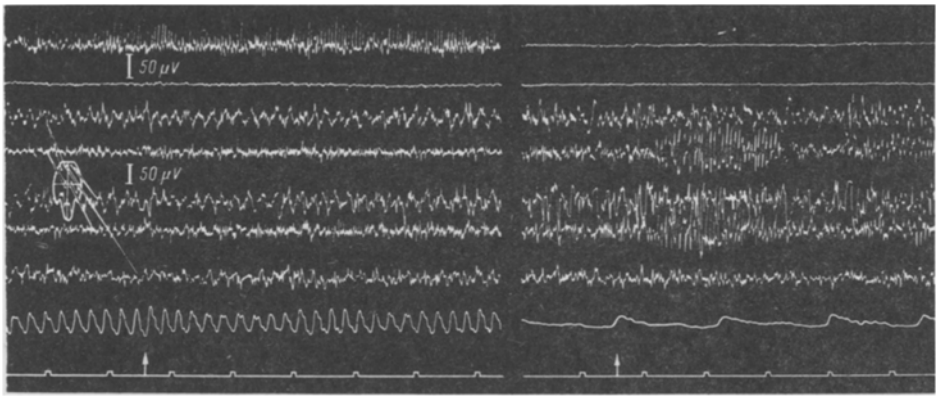

Fig. 3. Reaction to sound stimulation in a rabbit with local tetanus of the left hind leg before administration of andaxin (A) and after, in a dose of 310 mg/kg perorally (C). The meaning of curves (top down); EMG of left and right gastrocnemius muscles, EEG of right occipital, right motor, left occipital, left motor regions of cerebral cortex, mesencephalic reticular formation; respiration, time marker (1 sec). The moments of sound stimulation are designated by arrows.

The threshold of sound stimulation that caused the "activation" reaction in the EEG markedly increased after administration of andaxin (Fig. 3A, C).

We did not note essential disorders in respiration and cardiac activity. We observed only a certain decrease in the respiration rate and of the cardiac rhythm, which was accompanied by a drop of the rectal temperature of the animals within limits of 0.2-0.8°.

Relaxation of the muscles lasting 5-6 h was established in some of the rabbits after the administration of andaxin. Certain animals lost the ability to move, and lay on their sides.

The administration of large doses of andaxin (500-650 mg/kg) to the rabbits caused a more evident and prolonged relaxation of the muscles which was attended by a decrease in their electrical activity. The animals lay down and could not move. The changes in the EEG upon administration of large doses of the preparation were diphasic. At first they had the same character of in the animals of the previous group. After 1.5-2 h the EEG became typical for the state of excitation of the cerebral cortex and remained such for 2-3 h.

DISCUSSION

On changing to a discussion of the presented experimental material it is fitting to note first of all the prolonged (up to 4 h and more) effect of the indicated doses of andaxin.

This circumstance together with the absence of respiratory and cardiac disorders when using the preparation permits us to use its systematic administrations to achieve a prolonged ataractic effect in tetanus.

The mechanism of action of andaxin in this disease differs from the action of other relaxants used in its treatment.

Whereas curariform agents [2], chlorpromazine [1], and chloral hydrate rapidly lower the electrical activity of tetanus-affected muscles, andaxin at first does not have a substantial effect on it. Along with this it eliminates enhancement of the electrical activity in response to stimulation of the mesencephalic reticular formation. Here the preparation evidently does not have an inhibiting effect on the reticular formation itself, since its threshold stimulation was accompanied by the usual "activation" reaction in the EEG which indicates retention of normal excitability and on activating ascending effect on the cerebral cortex. It is natural to assume that there were also descending effects of the reticular formation, but apparently they were blocked somewhere on the pathway to the motoneurons of the spinal cord. Most probably this blocking of the ascending reticular effects caused by andaxin occurred at the level of the intercalary neurons of the spinal cord, through which the effects are usually accomplished and on which, in turn, the drug acts. The subsequent drop in excitation in the spinal motoneurons, manifested as disappearance of

electrical activity of the muscles affected by tetanus, can also be caused by the primary action of andaxin on the intercalary neurons which, as is known, play an important role in the pathogenesis of tetanus [3, 4, 8].

From what has been stated we can consider andaxin as one of the drugs for the pathogenic therapy of tetanus.

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