EXPERIMENTAL BASIS FOR AMINAZINE THERAPY IN TETANUS

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In recent years, aminazine, known abroad under the names chlorpromazine, megaphene, or largactyl, has been used in clinical practice in a number of nations, including the Soviet Union, for treating patients with tetanus [6, 11, 12, 15, 16].

The use of this preparation in the therapy of tetanus arose, apparently, on a purely empirical basis, in order to widen the circle of its activity against seizure states of varying etiology. The mechanism of its action in this illness has remained unclear up until the present, and has been explained by the majority of authors as a result of aminazine's capacity to reduce the tonus of skeletal muscles.

However, as shown by contemporary pharmacodynamic investigations, the actual influence of aminazine on the tonus of striated muscle is rather complicated. A number of investigators have established that aminazine does not reduce the amplitude of muscular contractions in response to stimulation of the corresponding peripheral segment [5, 7]. The investigations of N. A. Kruglov [4] also showed that aminazine does not cause noticeable functional shifts at the level of the segmental structures of the spinal cord. This is proven by the great stability in the magnitude of the mono- and polysynaptic reflexes, observed in conjunction with the action of this drug in a wide range of doses.

The data presented from the literature indicate that relaxation of skeletal muscles, occurring under the influence of aminazine, is caused by its action on the supraspinal divisions of the central nervous system. According to the viewpoint of a number of investigators, aminazine shows a selective action on the reticular formation of the brain stem, blockading its ascending and descending effects [1, 2, 4, 8, 10, 13].

In light of these data, a question naturally arises in regard to the character of aminazine's activity in tetanus. From clinical observations, it is known that in this illness aminazine demonstrates a rather prolonged pacifying effect on the patients, accompanied by easing of the tension in the muscles involved by the disease process. Its therapeutic effect is explained by this.

It has been shown experimentally that the injection of aminazine into animals suffering from tetanus intoxication reduces the electrical activity in the reticular formation of the brain stem [9]. This afforded a basis for postulating that the therapeutic action of aminazine in tetanus is related to its influence on that portion of the brain. However, the character of this influence has remained unstudied until the present time.

This work is devoted to studying the mechanism of action of aminazine in tetanus.

METHOD

The present investigation consists of two basic parts. The first of these is designed to study the role of the reticular formation of the brain stem in the genesis of motor disturbances associated with tetanus, the second—to study the experimental therapy of these motor disturbances with aminazine.

A total of 32 adult rabbits of the chinchilla family were placed under observation, weighing 2.5—3 kg. Tetanus was induced in the animals by the intramuscular injection of a minimum lethal dose of tetanus toxin into one of the posterior or anterior extremities. Observations were carried out on the rabbits on a long-term basis, using electrodes inserted into the brain. The operation by which the electrodes were inserted was performed by indirect orientation, according to the schema of Gangloff and Monnier [14]. The position of the electrodes in

mid-brain was verified in cross sections of this area at the end of the long-term experiments. At different periods of the tetanus intoxication, the rabbits were studied for changes in the bioelectric activity of the muscles (EMG), in the cerebral cortex (EEG), in the reticular formation of the mid-brain, in the EKG, and in respiration.

Conduction of the biopotentials was accomplished by means of bipolar electrodes in the unanesthetized animals, the latter being kept in a darkened, screened, chamber. Amplification and recording of the biocurrents were carried out with the aid of an eight-channel encephalograph of the "Kaiser" brand, at a frequency range of 0.2–500 cps.

The aminazine was injected intravenously, in doses of 5–10 mg per kg of weight of the animal. In a series of experiments, we stimulated the reticular formation of the mid-brain with electrical stimuli at a frequency of approximately 200 cps, lasting 1 millisecond, with a force of 1–3 volts.

RESULTS

In the first part of the investigation we studied the role of the reticular formation of the mid-brain in the pathogenesis of tetanus.

As we know, the disease is accompanied by elevation of the electrical activity in the muscles, which begins with its incubation period, attains its maximum intensity at the time of its local manifestations, and dwindles in the late stages of the tetanus intoxication [3].

In the incubation period of the illness, the electrical activity within the muscles in the region of the tetanus toxin injection is distinguished by its variability. It is markedly strengthened during application of any kind of stimuli to the animals, as well as at the moment of their motor excitation. It is reduced under conditions of complete rest.

Thanks to the simultaneous recording of the EMG, cortical EEG, electrical activity of the brain stem reticular formation, EKG and respiration, we succeeded, in our experiments, in establishing that the elevation in the electrical activity of the muscles damaged by tetanus, at early periods in the illness, depended on the influence of the brain stem reticular formation.

The observations performed by us on rabbits showed that, while in normal animals electrical stimulation of the reticular formation of the mid-brain, accompanied by the characteristic changes in the EEG, did not cause changes in the starting EMG, in rabbits with tetanus intoxication it caused a marked increase in the electrical activity of the muscles involved in the disease (Fig. 1).

This enhancement of the electrical activity in the muscles in response to stimulation of the reticular formation considerably exceeded the duration of the changes in the EEG, and was more clearly manifested in the early periods of the tetanus intoxication: in the incubation period of the illness and at the stage of the appearance of local tetanus.

Periods of spontaneous changes in the EEG and EMG also appear to be characteristic for these stages of the illness, and are similar to those which take place during stimulation of the brain stem reticular formation (Fig. 2a). Such changes in the EEG and EMG coincided temporally with the clear rhythm "regulation" of the potentials in the reticular formation characterizing its excitation state. Such interlinked changes in the electrical activity of the brain stem reticular formation, the cerebral cortex, and muscles are observed in animals in association with the most diverse stimuli: sound, tactile, pain (Fig. 2b). With frequent application of these stimuli, a constant background of elevated electrical activity in the muscles involved by tetanus is observed in the animals, accompanied by activation of the cerebral cortex.

In the period of generalized tetanus, characterized by a reduction in the electrical activity of the muscles, stimulation of the mid-brain reticular formation, accompanied by a corresponding reaction in the EEG, caused only a very brief intensification of the electrical activity in the muscles.

From the observations presented in the first part of the investigation, it follows that excitation of the brain stem reticular formation caused by an electrical current or different adequate stimuli is accompanied, in animals with tetanus intoxication, by a marked and prolonged elevation of the electrical activity in the muscles involved by tetanus.

Thus, the brain stem reticular formation, constantly being excited under the influence of afferent stimuli of the most diverse natures bombarding the organism under the normal conditions of its existence, protects its race by the "transformation" of these stimuli into a motor act at the periphery.

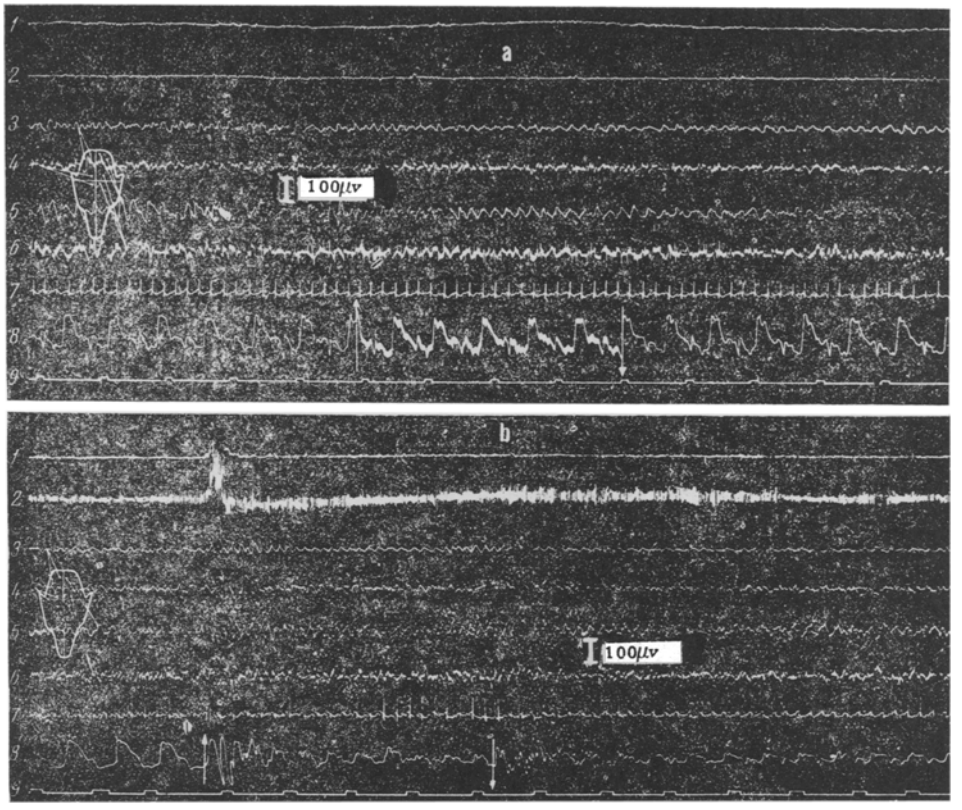

Fig. 1. Experiment involving stimulation of the reticular formation of the mid-brain in rabbit No. 732 before injection of the toxin (a) and during the incubation period of tetanus caused by the injection of 1 DLM of tetanus toxin into the left gastrocnemius muscle (b). Meaning of the curves (from above downward): electrical activity of the right gastrocnemius muscle, left gastrocnemius muscle, right occipital, right motor, left occipital, left motor, regions of the cerebral cortex; EKG; respiration; time markings (1 second). Initiation and termination of stimulation of the reticular formation are designated by arrows.

Experimental data obtained in this part of the investigation reveal one of the pathways by which nonspecific afferent stimuli participate in the pathogenesis of tetanus.

As we know, in the development of this pathological process, afferent stimuli hold an essential pathogenetic importance. This is supported by the intensification of a spasm attack in patients with tetanus in response to any stimulus: sound, tactile, etc. However, until the present time the mechanism of action of these stimuli remained unelucidated, and was regarded as stemming from a generalized elevation in the reflex excitability of the organism.

According to our impression, our data cast light on the mechanism of these phenomena, and further develop the concept of Academician A. D. Speranskii on the role of the nonspecific nerve component in the development of pathological processes, even those in which a specific beginning is beyond doubt.

The second part of the investigation was designed to study the mechanism of aminazine's therapeutic action in tetanus. In this case, it was shown that intravenous injection of aminazine into the "tetanic" rabbit caused relaxation of the muscles that were in a state of rigidity, accompanied by a lowering of their electrical activity.

Aminazine showed a varying influence on the electrical activity of the cerebral cortex of the rabbits, depending on the stage of the illness. In early periods of the disease (incubation, local tetanus) this influence was more significant, and was manifested by a marked shift in the spectrum of frequencies of the potentials composing the EEG in the direction of slow waves. At later stages of tetanus, local or systemic, these shifts in the EEG were considerably less apparent and appreciably briefer. They only occurred with doses of aminazine such, that injection caused pronounced disturbances in cardiac activity and rapid death of the animal.

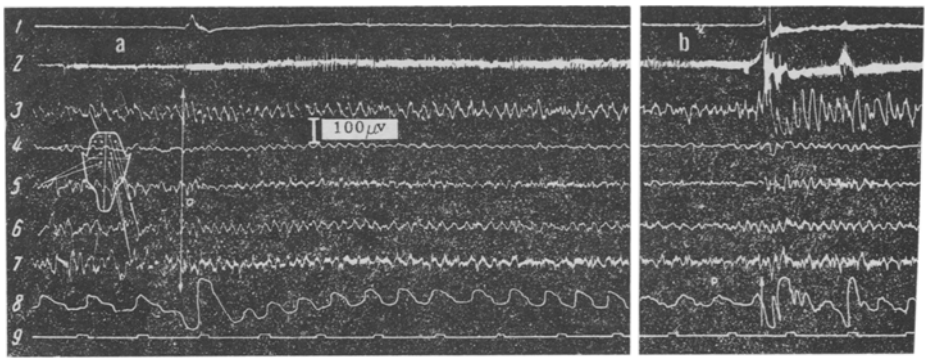

Fig. 2. Changes in the EEG and EMG in rabbit No. 732 during the incubation period of tetanus caused by injection of 1 DLM of tetanus toxin into the left gastrocnemius muscle—spontaneous (a); at the moment of a painful stimulus, indicated by the arrow (b). Meaning of the curves (from above downward); electrical activity of the right and left gastrocnemius muscles, reticular formation of the mid-brain, right occipital, right motor, left occipital, left motor regions of the cerebral cortex; respiration; time markings (1 second).

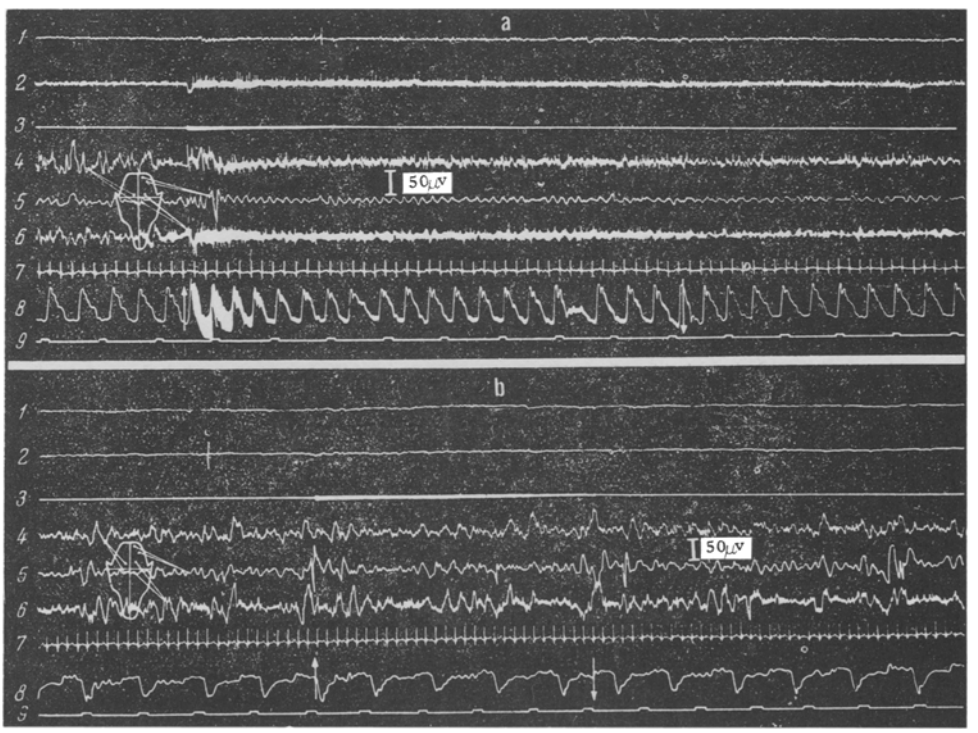

Fig. 3. Experiment involving stimulation of the reticular formation of the mid-brain in rabbit No. 934 with local tetanus of the left posterior extremity: (a) before the injection of aminazine; (b) after intravenous injection of aminazine in a dose of 10 mg/kg. Meaning of the curves (from above downward): electrical activity of the right and left gastrocnemius muscles; line corresponding to the disconnected EEG, right motor, left occipital, left motor regions of the cerebral cortex; EKG; respiration; time markings (1 second). Initiation and termination of stimulation of the reticular formation are designated by arrows.

Particular interest is aroused by the fact that injection of aminazine was accompanied, in all cases, by disappearance of the above-described intensification in the electrical activity of the muscles involved by tetanus, that occurs in response to stimulation of the brain stem reticular formation (Fig. 3).

Simultaneously, activation of the cerebral cortex, characteristic for this stimulation, also disappeared, which serves as evidence for blockade of both the descending and ascending effects of the reticular formation.

The injection of aminazine into the tetanus-intoxicated animals, therefore, eliminated the participation of the nonspecific effects in the formation of the tetanus symptom complex, which would otherwise be accomplished through the reticular formation of the brain stem. Apparently, this mechanism is fundamental to the action of aminazine in tetanus, which also is indirectly confirmed by its more apparent action on the cerebral cortex in the early periods of the illness, when the ascending and descending effects of the reticular formation would be more significant.

It would seem to us that the presented data justifies the assertion that the use of aminazine in the therapy of tetanus has a pathogenetic basis, and, apparently, it may be postulated that it should be more effective in the early periods of this illness.

SUMMARY

Chronic experiments were performed on rabbits with electrodes implanted into the brain. The role of the brain stem reticular formation in the origin of motor disturbances in tetanus was established. As demonstrated, aminazine blocking the effect of the stem reticular formation eliminates the participation of nonspecific afferent stimulations (such as sound, tactile, etc.) in the symptom complex of tetanus; this evidently conditions the mechanism of its therapeutic effect in this disease.

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