ROUTES OF ENTRANCE OF TETANUS TOXIN INTO THE CENTRAL NERVOUS SYSTEM AND CERTAIN QUESTIONS IN THE PATHOGENESIS OF EXPERIMENTAL TETANUS

IV. ON THE PATHOGENESIS OF ASCENDING AND DESCENDING TETANUS

G. N. Kryzhanovskii, L. A. Pevnitskii, V. N. Grafova, and A. A. Polgar

From the Laboratory of Infectious Pathology (Head—Corresponding Member of the Akad. Med. Nauk SSSR, Professor A. Ya, Alymov) of the Institute of Normal and Pathological Physiology (Director—Active Member of the Akad. Med. Nauk SSSR, Professor V. V. Parin) of the Akad. Med. Nauk SSSR, Moscow. Director of the Project—Candidate of Medical Sciences G. N, Kryzhanovskii.

(Presented by Active Member of the Akad. Med. Nauk SSSR, V. V. Parin)

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In previous investigations [14-17], it was shown that in animals of different species—white rats, guinea pigs, rabbits, cats, dogs, and apes—tetanus toxin infiltrates through the muscles into a nerve trunk, advances along the trunk in the central direction, and enters the spinal cord via the anterior roots.

In all the enumerated animal species, the experimental tetanus followed the pattern of the so-called ascending type: initially, local tetanus arises in the extremity which was injected with the toxin, following which the systematic symptoms develop in the form of spasm of the muscles in the trunk, neck, extremities, and fits of generalized convulsions. However, in man [10, 18, 19, 20] and certain agricultural animals [3, 9], tetanus usually follows the pattern of the so-called descending type. In this form, the illness immediately begins with trismus and generalized rigidity; the symptoms of local tetanus are not observed. The question arises as to whether the indicated pathway of the toxin’s entrance into the central nervous system takes place in those cases where the tetanus develops according to the descending type. Resolution of this question can be of major importance in understanding the pathogenesis of tetanus in man. This thus determined the basic purpose of the present work.

The goal of this investigation was to compare the characteristics of the clinical forms of the illness, and the routes of entrance of the tetanus toxin into the central nervous system.

METHOD

The investigations were carried out on donkeys, in whom, as in the case of horses [3, 22], the injection of a lethal dose of toxin leads to the development of tetanus of the descending type. Toxin (series 589, ëM Akad. Med. Nauk SSSR), in a dose of 15 DLM (equal to 0.005 mg/kg, a total of 2 to 10 mg per animal) and a volume of 2 ml, was injected into the posterior muscle group of the left shank. 24-48 hours after the injection of toxin, the animals were sacrificed by either electrocution or exsanguination. For tetanus toxin determination we selected the following nerve structures: anterior and posterior roots of the spinal cord (L4 and L5 and C5—C8) on both sides, the spinal ganglia of the same segments, the sensory portion of the left sciatic nerve (the bundle of fibers taking their beginning from the spinal ganglia L5 and L4), the distal, middle and proximal portions of the left, and distal portion of the right, sciatic nerve, the sensory and motor (innervating the masticatory muscles) portions of the trigeminal nerve, the sensory roots of the trigeminal nerve entering the medulla oblongata, and the Gasserian ganglia. From the tissue of these structures, we prepared homogenates which we injected into mice in the muscles of the posterior extremity (60 mg of tissue per 0.6 ml of homogenate). The concentration of toxin in the homogenates was judged by the severity of the illness in the mice. In addition, using the method of biological titration in the mice, we investigated the concentration of toxin in blood drawn at the time of the animals' death. A more detailed description of the method used in the experiments has been given in an earlier report [15].
Besides determining the toxin in the indicated tissues, we studied the clinical course of the illness. In special experiments, we recorded the electrical activity in the muscles of the posterior extremities, using a myograph ("Elema" company) in which two channels were amplified by supplementary cascades. Conduction of the biocurrents was done via needle electrodes.

RESULTS

Donkeys are comparatively sensitive to tetanus toxin: the minimum lethal dose (DLM) for them, causing death on the fourth day, was 70 mice-DLM/kg of body weight, according to our data. However, animals died of tetanus after the injection of 1/10–1/20 DLM, and even smaller doses of toxin. The sensitivity of donkeys to tetanus toxin, apparently, approximates the sensitivity of horses [3, 24].

Following the injection of a lethal dose of toxin (1/3–2/3 DLM) into the muscles of the posterior extremity, symptoms of generalized rigidity arise in the animal after several days (usually after 2–4 days, depending on the dose of toxin), along with difficulty in locomotion and mastication. No signs of local tetanus are observed (Fig. 1a). The symptoms then rapidly progress, the trismus is intensified, and there is marked tension in the muscles of the neck, ears, trunk and extremities (the latter are held as straight as sticks) (Fig. 1b). Against this background, there arise paroxysms of generalized seizures. Thus, with the injection of sufficiently large doses of toxin, the illness, in donkeys, progresses along the lines of the descending type, with no manifest signs of local tetanus.

Fig. 1. Clinical picture of descending tetanus in the donkey, following the injection of 2/8 DLM of toxin into the muscles of the left shank. a) Appearance of general rigidity (6th day of illness); b) generalized tension in the muscles of the trunk, neck, ears, and extremities (7th day of illness). Death occurred on the 9th day following injection of the toxin.

Determination of tetanus toxin in various divisions of the peripheral nervous system showed (Table 1) that the toxin is found, with sufficient constancy, in the anterior roots and the sciatic nerve on the side of the injection. Tetanus toxin is only observed in the anterior roots and sciatic nerve of the contralateral side in isolated cases (apparently, the result of some unaccounted conditions or of peculiarities in the animals; the difference in the results of these determinations was statistically significant). These data indicate that the presence of toxin in the nerve and the anterior roots on the side of the injection is not related to its infiltration from the blood into the indicated structures, but to its advancement from the muscles along the nerve trunk.

In addition, the toxin is gradually observed in the spinal ganglia, both on the side of injection and on the contralateral side; it also gradually appears in the ganglia of the cervical segments, and in the Gasserian ganglion. This indicates that the tetanus toxin enters the ganglia from the blood. A similar mechanism takes place in dogs [17]. The detection of tetanus toxin in the posterior roots on the same side as the injection, in half the number of cases, compels one to conclude that in certain animals it can also enter the posterior roots. In the majority of cases (in 5 out of 7), it was possible to detect toxin in the motor portion of the trigeminal nerve innervating the masticatory musculature. These data are proof that the toxin can enter the motor portion of a mixed nerve from the blood, and advance along bundles of motor fibers.

Thus, the experiments involving determination of the tetanus toxin in various divisions of the peripheral nervous system showed that in donkeys, just as in other animals [15, 16, 17], the tetanus toxin enters from the muscles into the corresponding nerve, and, subsequently, into the anterior roots of the spinal cord. However, the question