CENTRAL NERVOUS CHANGES IN EXPERIMENTAL TETANUS AND THE MODE OF ACTION OF THE TETANUS TOXIN

COMMUNICATION II. THE PART PLAYED BY SPINAL MECHANISMS

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In previous articles [5, 6] we have described the characteristic irradiation of excitation in the central nervous system of animals infected with general ascending tetanus. The characteristic feature of this phenomenon in the development and generalization of excitation in the central nervous system is facilitated by applying various stimuli to the limb into which the tetanus toxin was injected; (in future, for convenience this will be referred to as the "tetanized" limb). When similar stimuli are applied to other parts of the body, including the opposite limb, which was also involved in the pathological process (segmental tetanus) the spread of the excitation along the central nervous system was either poorly shown, or did not occur at all. The investigations showed [5, 6] that the phenomenon cannot be due to any peripheral mechanism, such as, for instance, an increased excitability of the receptors of the "tetanized" limb, which would cause additional central nervous stimulation.

The present work concerns a further analysis of the phenomenon described. The problem is to explain the part played by the facilitatory mechanisms described above in the development of spasms induced by stimulating the tetanized extremity, and to investigate the involvement of other parts of the nervous system, in particular the dorsal root ganglia. Solution of these problems is of interest from the neurological standpoint, as it concerns the spastic syndrome characteristic of tetanus.

METHOD

The experiments were carried out on white rats weighing 140-160 g. In order to eliminate suprasegmental influence, we divided the spinal cord [21] between C_4 and C_5. Under these conditions, natural breathing is maintained. To eliminate the influence of the spinal ganglia conveying afferent stimuli to the cord, the normal stimulation from the receptors was replaced by electrical stimulation of the central ends of the cut dorsal roots. The dorsal roots of L_4 to S_1 were cut, and in several experiments those of L_3 and S_2 were also divided, thus interrupting the sensory inflow from muscles innervated by the sciatic nerve. Stimulation was applied to L_5 or L_6. Section of the spinal cord and dorsal roots was made under a brief ether anesthesia; during the experiment, careful experiments were made on the excitability of the spinal cord, and care was taken to avoid cooling or damaging the animal unnecessarily; in many experiments, the spinal cord was surrounded with vaseline.

The experiments were carried out during the development of ascending generalized tetanus several days after injecting 3 times the minimum lethal dose (MLD) into the muscle of the left hind limb which is innervated by the sciatic nerve (gastrocnemius and posterior thigh muscles). Simultaneously with the toxin, 0.025 active units (AE) of serum were injected. Other details of the method have been described in detail in [5].

RESULTS

Tests have shown that section of the spinal cord has no appreciable effect on the appearance of the phenomena described: just as before section, application of various stimuli to the tetanized limb (pressing on the muscle, tendon, or foot; bending the paw; pinching the skin of the pad of the foot, etc) induced the characteristic onset of generalized tetanic convulsions embracing all muscles of the trunk and limbs lying distal to the point at which the cord was sectioned. During this time, in the muscles referred to, a powerful volley of electrical impulses was recorded. The upper two traces in the drawing show the electrical activity in the muscles of the right thigh during a convulsion induced by pressing the paw of the tetanized limb. Similar pressure on the opposite (right) paw caused only a local response consisting of a withdrawal of the foot and the appearance in the muscles of a short-lasting and comparatively small burst of electrical activity (see lowermost trace of figure).

Thus, after elimination of the higher nervous centers, stimulating the tetanized limb causes a generalized excitation throughout the whole spinal cord involving remotely placed motor neurons. A particular feature of this reaction is the long after-effect and the slow extinction of the electrical activity, with separate repeated after-bursts (see Figure, A). The latter occur particularly frequently in the muscles of the opposite hind limb, but also may frequently be recorded simultaneously in different muscles of the trunk and limbs, thus indicating a snychronization of the bursts of excitation of the motor neurons in different segments of the spinal cord.

These features of the reaction, i.e. , the low threshold, high intensity, and involvement of different muscle groups including antagonist muscles, the long after-effect, the slow extinction, the appearance of repeated "spontaneous" discharges of motor neurons, and the synchronization of the bursts of their excitation, represent features characteristic of spasticity [17, 18]. G. Magoun and other workers [18, 21, 22] have shown that an important part in the development and maintenance of this condition is played by the supraspinal structures, in particular by the reticular formation of the brainstem. Our results show that this phenomenon may be brough about by the intraspinal mechanisms without the participation of the suprasegmental facilitatory influences. It does not follow, of course, that supraspinal mechanisms play no part in tetanic convulsions. This problem will be investigated separately.

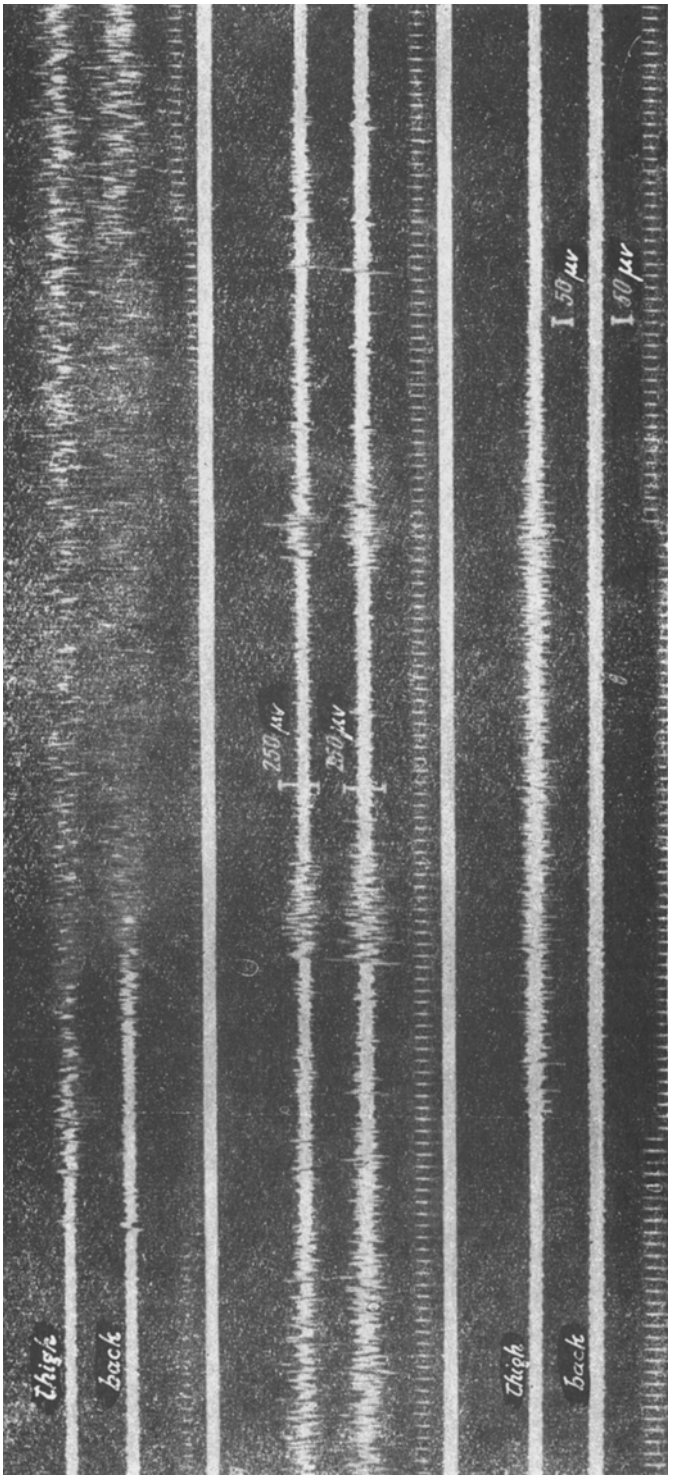
Experiments in which the central ends of the cut dorsal roots were stimulated while the cord was intact showed that stimulation of L_5 or L_6 on the left side, which was the side in which the toxin injection was given, caused a typical attack of tetanic convulsions with a high level of electrical activity in the different muscles of the trunk, neck, and limbs; there was a long after-effect with repeated bursts of impulses. The tetanic reaction could be induced even with very mild stimulation, it always became generalized, and when the tetanus infection was severe it always appeared immediately at maximum strength. When a similar stimulus was applied to the central ends of the cut roots of the opposite side, there was only a small response, and in order to invoke a generalized spasm, the strength of the stimulus had to be increased considerably. However, in the latter case the convulsion was much weaker than when the roots on the tetanized side were stimulated.

The experiments showed, therefore, that even with direct afferent stimulation of the spinal cord without any possible participation of the spinal ganglia, the development of a generalized spasm is facilitated, i.e. , there is a facilitation of the spread of excitation along the central nervous system when the stimulus is applied on the tetanized side. Owing to section of the dorsal root, any positive feedback from muscles innervated by the sciatic nerve and into which the tetanus toxin had been injected was eliminated; the phenomenon cannot therefore be due to any additional proprioceptive stimulation corresponding to a servo-reflex based on feedback.

The results obtained agree entirely with previous investigations [5, 6] and indicate that the phenomenon is due to changes in the functional condition of the central reflex apparatus at spinal cord level.

If, however, we accept the present day views on the mechanism of action of the tetanus toxin, according to which this exerts its selective effect on motor neurons [8, 9, 12, 19], it is then difficult to explain the phenomenon, since motor neurons represent the final common path of reflex arcs. An increase of general reflex excitability, which might be associated with the generalized involvement of motor neurons, would obviously be of considerable importance in connection with the phenomenon described, since the latter develops only during the stage of geralized tetanus. However, this mechanism alone cannot be responsible for a selective facilitation of the development of convulsions caused by stimulating the tetanized limb.

Evidently the cause of the phenomenon must lie in the changed functional condition of those limbs of the reflex arc which receive and transform the afferent impulses entering the spinal cord via the dorsal roots and which transmit them to different levels of the central nervous system.



Electrical activity in muscles of the posterior group of the right thigh (upper trace in all oscillograms) and in the back muscles of the right side (lowermost curve in all oscillograms) in rats with spinal cord section; excitation was caused by pressure on the left foot (top two traces) and right foot (third trace). Time marker — 20 mseconds. Displacement of the time marker indicates period of applying pressure to the foot. (Second trace represents continuation of first). Experiment on 12/18 1957. Rat No. 2.

Descriptions have recently appeared [11, 13, 14, 16] which indicate the presence of special regulatory mechanisms determing the extent of the afferent stimulation to the cord; control over these mechanisms is exerted by inhibitory processes originating in the internuncial neurons of the posterior horns of the spinal cord. It is probable that in the development of tetanus such regulatory mechanisms are disturbed, and that as a result the whole of the afferent stimulation from the "tetanized" limb enters the spinal cord unchanged. At the same time, the possibility cannot be excluded that at an early stage in generalized tetanus there is also reciprocal inhibition of other forms of afferent stimulation (for instance, that from the opposite side), and that this accentuates the difference between the two sides. Subsequently, during the development of generalized tetanus and the destruction of all inhibitory processes, the asymmetry becomes somewhat reduced.

Also, the type of electrical activity developed, the long duration of the after-effect, the gradual decay of the excitation with separate repeated bursts, and the very high intensity of the reaction in response to comparatively weak stimulation, all suggest that an important part must be played by the large number of internuncial neurons of the cord which could bring about a prolonged increased stimulation of the motor neurons.

At present it is difficult to say which neurons play the part of "dispatching stations", and whether they lie in the substantia gelatinosa of the cord [20] or in the grey matter [10] where they would appear to act as collectors of different stimuli [15]. This problem will be the subject of further investigation.

From the neurological standpoint, it is clear that in the development of ascending generalized tetanus, a new form of central relationships are involved. The group of internuncial neurons on the "tetanized" side act as "dispatching stations" and form new functional relationships with the rest of the cord, being enabled, as it were, to send on stimulations unrestricted to all levels. The phenomenon described may have something in common with other forms of functional connections, for instance Ukhtomskii's dominance [7], Wedensky's hysteriosis* [1-4] and others); at the same time, however, the phenomenon differs from these others by special features which emphasize its distinct nature and allow it to be distinguished from many other neurological phenomena.

SUMMARY

Spread of the excitation along the spinal cord was studied in white rats in ascending general tetanus. The special feature of this phenomenon is that the excitation becomes generalized completely (in some cases only) on stimulating the limb into which the lethal dose of toxin had been injected. The clinical effect takes the form of a convulsive attack with characteristic features of spasticity. High division of the spinal cord had no appreciable effect on the phenomenon.

The same effect was observed on stimulating the central ends of the cut dorsal roots on the side of the toxin injection.

Synchronization of the bursts of excitation occurred in remote groups of motor neurons located in different segements of the cord.

The part played by the various types of internuncial and motor neurons of the spinal cord is discussed. It is suggested that neurons functioning as "dispatching stations" may play a special part.

LITERATURE CITED

[1] E. Sh. Airapet'yants, Transactions of the VMMA (Naval Medical Academy)*, volume 17, p. 54 (1949).

[2] O. A. Andriainen, Reports of the AN SSSR*, volume 70, No. 2, p. 331-334 (1950).

[3] N. E. Vvedenskii, Russkii vrach, No. 22, 1912 (Complete Collected Works*, volume IV, p. 325 (1953)).

[4] I. A. Vetyukov, Transactions of the VMMA (Naval Medical Academy)*, volume 17, p. 95 (1949).

[5] G. N. Kryzhanovskii, Byull, éksptl. biol. i med., No. 12, pp. 43-51 (1957).

[6] G. N. Kryzhanovskii, in book: Modern Problems of Nervism in Physiology and Pathology*. Moscow, 1958, p. 582.

[7] A. A. Ukhtomskii, The Nature of Dominance,** Complete Collected Works, volume 1, 1950.

[8] J. J. Abel, W. M. Firor and W. Chalian, Bull. Johns Hopkins Hosp., 1938, v. 63, p. 373.

*Name not verified.

**In Russian.

[9] V. B. Brooks, D. R. Curtis and G. C. Eccles, J. Physiol., 1957, v.135, p.655.

[10] S. Cajal-Ramon, Histologie du systeme nerveuse de l'homme et des vertebres, 1952, t. 1, p. 532.

[11] G. P. Couch and G. M. Austin, J. Neurophysiol., 1958, v.21, N. 3, p. 217.

[12] U. Friedemann, A. Hollander and G. M. Tarlov, J. Immunol., 1941, v. 40, N. 3, p. 325.

[13] K. E. Hagbarth and D. G. Kerr, B. J. Neurophysiol., 1954, v. 17, p. 295.

[14] F. Kleyntjens, K. Koizumi and C. Brooks, Mc., C. A. M. A. Arch. Neurology and Psychiatry, 1955, v. 73, N. 4, p. 425.

[15] C. M. Kolmodia, Acta physiol. scand., 1957, v. 40, Suppl. 139, Stokholm, 89, pp.

[16] U. T. Lindblom and G. O. Ottosson, Acta physiol. scand., 1956, v. 35, b. 3-4, p. 203.

[17] D. B. Lindsley, L. H. Schreiner and H. W. Magoun, J. Neurophysiol., 1949, v. 12, N. 3, p. 197.

[18] H. W. Magoun and R. Rhines, Spasticity; The Stretch Reflex and Extrapyramidal Systems (Springfield: C. Thomas, 1947).

[19] H. Meyer and F. Raasom, Arch. exper. Pathol and Pharmak., 1903, Bd. 49, H. 6, S. 369.

[20] A. A. Pearson, A. M. A. Arch. Neurol. and Psychiatry 1952, v. 68, N. 4, p. 515-529.

[21] L. H. Schreiner, D. B. Lidsley and H. W. Magoun, J. Neurophysiol., 1949, v. 12, N. 3, p. 207.

[22] A. A. Ward Jr. J. Neurophysiol., 1947, v. 10, N. 2, p. 89.