CHANGES IN THE EFFERENT PATHWAY OF THE SPINAL CORD IN TETANUS POISONING

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At present time considerable neurological evidence has accumulated indicating that each relay station in the central nervous system is a complex apparatus which not only allows the passage but also regulates the rate of flow of impulses. This regulation is exerted as an innate mechanism, and is also subject to influences from other levels. Therefore in order to describe the working condition of the apparatus whose function it is to let through or to interrupt impulses, the most general functional description will be in terms of the proportion of the incident impulses which are passed.

The efferent outlet in the spinal cord is one of a number of specialized systems regulating the rate of flow of impulses. Its basic operating portion is built up of motoneurones which transform the train of impulses into the efferent outflow. It is known [4, 13, 14] that with orthodromic stimulation of a motoneurone,excitatory postsynaptic potentials (EPSP) may be generated at very high frequency, though the propagated action potentials are generated at a relatively low frequency.

This dissociation is associated with the after-hyperpolarization of the membrane of the motoneurone, which as has been shown [16, 17] develops after each action potential. A considerable proportion of the after-hyperpolarization consists of a secondary hyperpolarization developing as a result of the associated postsynaptic inhibition [17]. An important part in this connection is played by the so called antidromic or reverse inhibition which is brought about by the Renshaw cells through return collaterals of the axons of the motoneurones [15, 17-19, 23, 25]. The back-inhibition, during which the secondary hyperpolarization is most prolonged, is an important mechanism for restricting the frequency of discharge of mononeurones of the tonic apparatus. This special part in the regulation of activity of motoneurones also involves back-inhibition which occurs automatically after each, and particularly after each monosynaptic discharge of a motoneurone, and affects not only this motoneurone but neighboring motoneurones in the same group. Therefore back-inhibition is an inherent mechanism for the automatic regulation of the outflow.

The work of Eccles and his co-workers [11, 17], and that of other authors [6, 12, 27], and our own studies have shown that under the influence of tetanus toxin various kinds of postsynaptic inhibition of spinal motoneurones are impaired. It appeared therefore that during the action of tetanus toxin the outflow from any affected segment of the spinal cord should be increased.

The present work was undertaken in order to study the number of impulses passing through the spinal efferent pathway in tetanus.

EXPERIMENTAL METHOD

The conduction through the efferent pathway was estimated in terms of the monosynaptic responses to rhythmical stimulation of muscle afferents at various frequencies; we used either the tibial nerve, or branches running to both heads of the gastrocnemius muscle. Besides monosynaptic we also used polysynaptic stimulation which was

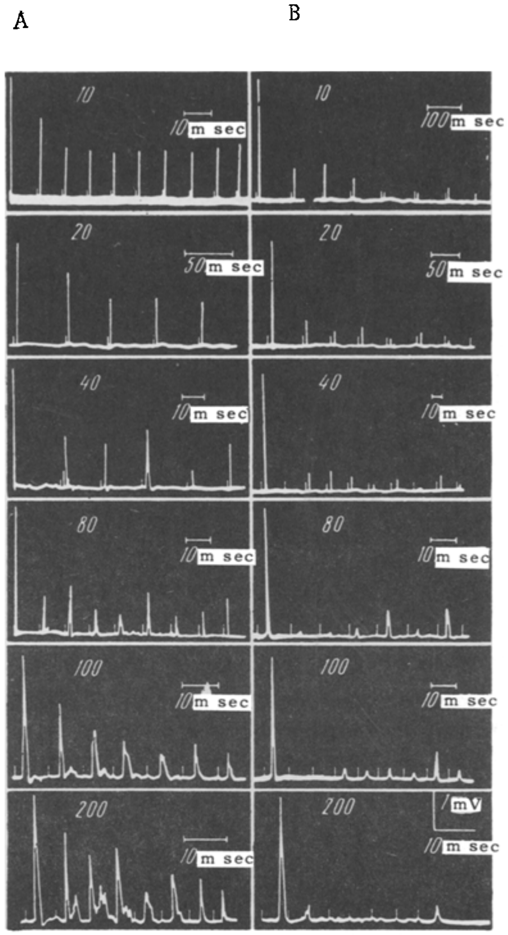

Fig. 1. Production of monosynaptic reflexes by stimulation of both branches of the nerve to the gastrocnemius muscle with stimuli of various frequencies, and of amplitude which is optimal for the elicitation of the monosynaptic response. A) Responses on the side into which the tetanus toxin had been injected (3rd day after injection of 1/20 MLD tetanus toxin); B) responses on the opposite side.

produced either by appropriate increase of stimulation of the mixed nerve, or by additional simultaneous stimulation of the cutaneous supply to the leg. The stimuli were square waves at a frequency of 10-200 cycles, given usually as a volley of 10.

Tetanus toxin was given in a dosage of 1/10, 1/100, and 1/200 MLD (for cat) and was injected into the gastrocnemius muscle. When the injection was given at this site, as our previous investigations had shown [5], the toxin enters the spinal cord through the ventral roots of L_7-S_1. By recording the potentials from these roots we were able to determine what changes occurred in the outflow from these segments.

The experiments were carried out on animals with a high spinal transection between C_7 and T_1;they were undertaken 2-6 days after injection of the toxin. Ether anaesthesia was used only for preparation of the animal and for transection of the spinal cord. Other manipulations, and the whole experiment were carried out without anaesthesia. To record the potentials we used an A.C.amplifier having a frequency range of 0.3-2000 cycles.

Altogether we used 30 animals.

EXPERIMENTAL RESULTS

With rhythmical stimulation of the muscle nerves under normal conditions, monosynaptic responses were inhibited at even quite low frequencies of stimulation (10-20 stimuli per second, or less). This result occurred in almost every case. Similar results have been obtained by other investigators [1, 2, 3, 24].

Under the influence of tetanus toxin the number of monosynaptic reflexes is increased (Fig. 1). However this increase is not always very marked. At a stimulus frequency of 100 cycles, a more marked increase of monosynaptic responses was found only in 7 out of the 13 cases. We must note that in these cases, although the stimulus remained at its previous value, during the rhythmical stimulation an additional polysynaptic flow of impulses was found to occur.

A different result was observed to be associated with combined mono- and polysynaptic stimulation (stimulation of the tibial nerve with maximum strength). Under these conditions the number of monosynaptic reflexes was greatly enhanced (Fig. 2). These reflexes were also observed at high stimulus rates of 100-200 per second, and they maintained a relatively high amplitude. This result was found in all cases, but in many of the experiments the monosynaptic responses were recorded at a stimulus frequency of 300 per second.

Similar results were obtained also in experiments in which additional polysynaptic stimulation was applied by stimulation of a cutaneous nerve (Fig. 3). Under these circumstances too, in most cases (in 5 of the 8 experiments) an increased outflow of monosynaptic responses was observed at a comparatively high stimulus frequency.

Thus with rhythmical monosynaptic stimulation through the efferent pathway as influenced by tetanus toxin, supplementary polysynaptic stimulation greatly increased the number of monosynpatic reflexes elicited. We must note that similar results have been obtained in our laboratory in experiments on white rats (V. K. Lutsenko). This leads us to suppose that the functional changes we have found in the system governing the outflow is part of a general pattern.

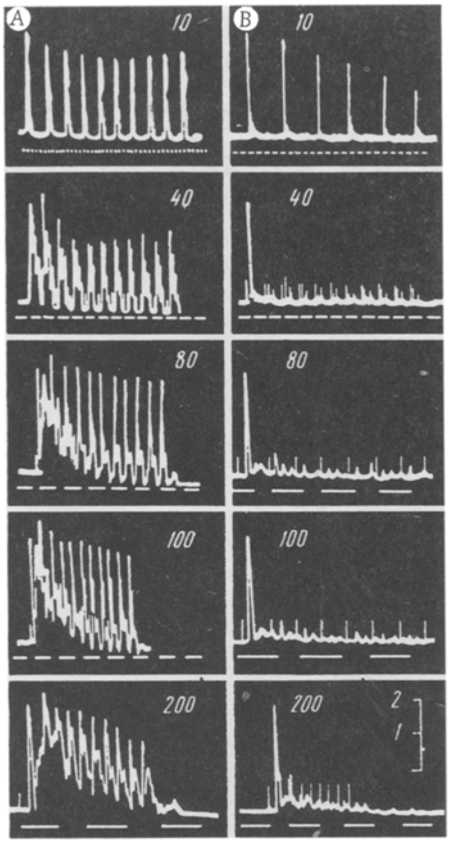

Fig. 2. Production of combined mono- and polysynaptic responses during maximal stimulation of a mixed nerve by stimuli at various frequencies. A) On the side of the toxin injection (5th day after the injection of 1/10 MLD); B) on the opposite side. Time marker 20 m seconds; amplitude calibration 1 mV.

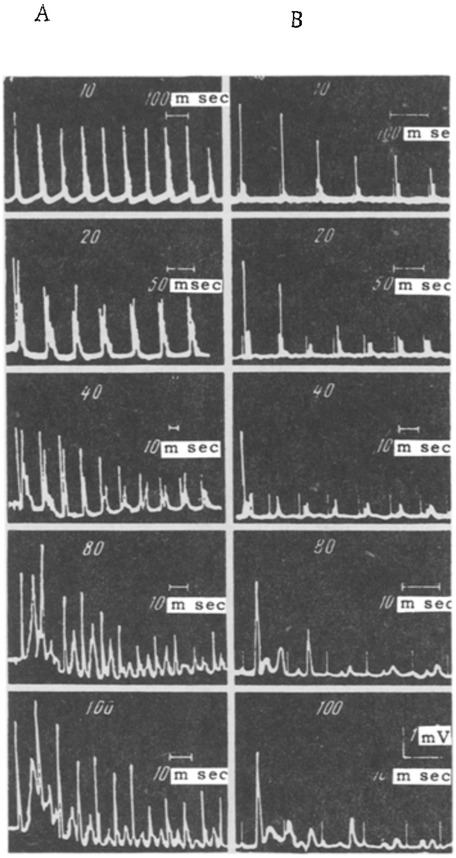

Fig. 3. Production of combined mono- and polysynaptic responses during simultaneous stimulation of a cutaneous nerve (maximal stimulus strength) and branching of the nerve to the gastrocnemius muscle (strength of stimulation optimal for the production of the monosynaptic reflex. A) In an animal infected with local tetanus (6th day after injection of 1/10 MLD of toxin); B) in a healthy animal.

From the results reported it can be seen that two mechanisms are responsible for the phenomenon of enhanced monosynaptic reflexes reflecting the increased power of the efferent domain to let through impulses: 1) disturbance of different kinds of postsynaptic inhibition of motoneurones, and 2) their supplementary postsynaptic activation).

By itself, elimination of postsynaptic inhibition of the motoneurones due to the influence of tetanus toxin is apparently insufficient to produce an effective increase in the number of impulses along the efferent route. Possibly this result is related to the maintenance of other kinds of regulation of the activity of the motoneurones during their rhythmical orthodromic stimulation including in particular processes occurring in the presynaptic apparatus [1, 3, 9, 13, 24].

An important condition of the increase in the number of impulses passed is the additional polysynaptic activation of the motoneurones. By depolarizing the membrane on the one hand this process interferes with postsynaptic (hyperpolarization) inhibition, and on the other increases the sensitivity of the membrane to orthodromic monosynaptic stimuli. Therefore if the passage of monosynaptic impulses appears also to be partially blocked on account of presynaptic suppression of the scatter of the impulses transmitted, this mechanism may be compensated by supplementary depolarization of the membrane brought about by polysynaptic stimulation. If the disturbance of the development of action potentials during rhythmic monosynaptic stimulation occurs in the membrane itself, in its electrically excitable part (as seems probable, because during rhythmical stimulation the EPSPs may be produced at a high frequency) [4, 13, 14], then in this case also supplementary polysynaptic activation will act as a facilitatory factor. It is known [8, 9] that supplementary depolarization of the membrane of the motoneurones increases their ability to generate action potentials in response not only to rhythmic orthodromic but to direct stimuli.

A point to note is that under the influence of tetanus toxin there is a marked increase of polysynaptic reflexes [6, 11, 12, 27], as is apparent from the results shown here (Fig. 2, A; Fig. 3, A). In such a case polysynaptic stimulation results in synchronized discharges of which the amplitude attains the level of monosynaptic spikes, and sometimes even exceeds such a level. Such polysynaptic activation brings about a very considerable depolarization of the membrane of the motoneurones, and establishes particularly favorable conditions for facilitation of the development of monosynaptic action potentials during rhythmical afferent volleys.

A fact which deserves attention is that under the influence of tetanus toxin polysynaptic afferent volleys which normally elicit a flexor reflex, now facilitate the development of extensor reflexes. This result signifies that the afferent systems of the flexor reflex terminate also on motoneurones of the extensors, probably through some kind of internuncial link. Normally their influence is not manifested because these same afferents also bring about inhibitory reactions through internuncial connections. When however the latter are eliminated the excitatory effects are revealed. We must note that even Sherrington [26] indicated the possibility of an extensor excitatory component in the flow of impulses elicited by stimulation of cutaneous and muscular nerves. In subsequent experiments many authors—in experiments which included a study of the activity of motoneurones—by means of micro-electodes have obtained results which confirm this hypothesis [28].

The results of our experiments show that under the influence of tetanus toxin there is a change in the way polysynaptic reflexes are elicited (see Figs. 2 and 3). It now becomes important to determine whether certain kinds of presynaptic regulation of the activity of the motoneurones is involved in the pathological process. Preliminary accounts have already been published concerning the condition of presynaptic inhibition of motoneurones produced by the tetanus toxin [7].

Thus the action of the toxin is to increase the flow of efferent impulses from the affected segments of the cord. It is not known whether the increased passage of impulses is due to the intermediate activity of groups of motoneurones contained within the same nucleus, or whether it is due to increase in the frequency of the discharges of each motoneurone. We do know that the action of strychnine is to disturb all kinds of postsynaptic inhibition and to increase the polysynaptic reflexes [11, 17]; the motoneurones may discharge at a high rate [9, 20, 22]. Very likely there is place for both mechanisms (we are currently studying this problem).

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.