SUPRASEGMENTAL INHIBITION AND FACILITATION AFTER INJECTION OF TETANUS TOXIN INTO THE MEDULLARY NUCLEI (THE SO-CALLED DISPATCH STATION PHENOMENON)

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Changes in descending inhibition and facilitation evoked by stimulation of the nucleus fastigii were studied after injection of tetanus toxin into the relay nuclei of the medulla in experiments on cats under superficial pentobarbital-chloralose anesthesia. Injection of tetanus toxin into these nuclei leads to an increase in their "functional dispatch." Descending inhibition (in response to injection of tetanus toxin into the gigantocellular nucleus) and descending facilitation (injection of the toxin into Deiters' nucleus and the nucleus ambiguus) were increased to many times their previous intensity, the latent periods of the descending effects were considerably shortened, their intensity rose sharply to a maximum, and their duration was greatly lengthened. To interpret these results it is postulated that powerful excitation generators are formed in the relay nuclei following disturbance of their inhibitory mechanisms. These results indicate that the "dispatch station" concept is applicable also to supraspinal structures.

KEY WORDS: tetanus toxin; suprasegmental inhibition and facilitation; gigantocellular nucleus; Deiters' nucleus; "dispatch station" phenomenon; excitation generator.

Previous investigations showed [7-9, 12, 13] that local poisoning of the spinal cord with tetanus toxin modifies inhibitory and facilitatory descending effects after stimulation of the medullary nuclei. However, virtually no attempt has yet been made to study whether tetanus toxin acts in this way on structures of the brain stem [14, 15, 23]. It was shown previously [2-6] that a so-called dispatch station (DS) can be created in various parts of the spinal cord with the aid of tetanus toxin, which disturbs various types of inhibition in the spinal cord [1, 3, 11, 17]. It was interesting to discover whether similar "dispatch stations" could be formed in the nuclei of the medulla.

These problems were the subject of the present investigation.

EXPERIMENTAL METHOD

Experiments were carried out on 32 cats weighing 2-4 kg lightly anesthetized with pentobarbital and chloralose (10 and 20 mg/kg, respectively). All the preliminary procedures were carried out under deep ether anesthesia several hours before the main experiment. Purified tetanus toxin,† in doses of 10-300 MLD for mice, was injected into the medullary nuclei in a minimal volume of fluid (1×10^{-4}-5×10^{-4} ml) with the aid of a special microinjector. Monosynaptic and polysynaptic reflexes from the ventral roots

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† The tetanus toxin was purified by O. P. Sakharova, a member of the laboratory staff.

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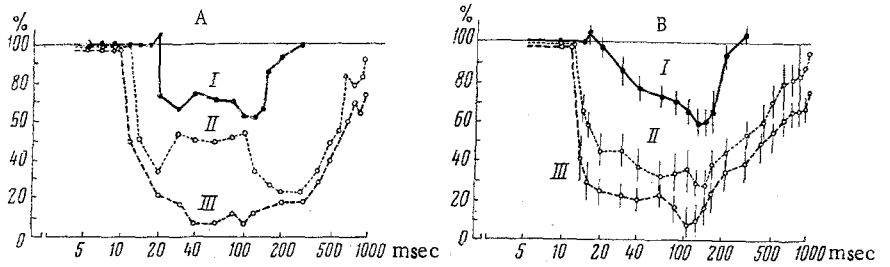

Fig. 1. Inhibition of polysynaptic reflexes induced by stimulation of nucleus fastigii strengthened after injection of tetanus toxin into gigantocellular nucleus in medulla. A) Descending inhibition of polysynaptic reflexes before (I) and 3 (II) and 24 h (III) after injection of tetanus toxin (90 MLD for mice) into gigantocellular nucleus (P7–L1–H3). Polysynaptic reflexes recorded from nerve to gastrocnemius muscle. Results of one experiment. B) General curves of suprasegmental inhibition of polysynaptic reflexes plotted from averaged data of 8 experiments (M ± m): I) before, II) 2 h and III) 4 h or more after injection of tetanus toxin (90 MLD for mice). Here and in Figs. 2 and 3: abscissa, time (in msec) between stimulation of nucleus fastigii and stimulation of muscular nerve (logarithmic scale); ordinate, magnitude of polysynaptic reflexes (in % of initial).

L5–S1 and from muscular nerves (nerve to gastrocnemius, deep peroneal nerve) in response to stimulation of these nerves by special buried block electrodes were recorded in the usual way. By the use of this technique, monosynaptic and polysynaptic reflexes could be recorded for a long period of time (24 h) during which the animal's condition remained good (trauma to the spinal cord and displacement and drying of the nerves were avoided). The degree of inhibition or facilitation was estimated from the amplitude of the reflexes, expressed in percentages of their initial level. The gigantocellular nucleus and vestibular nucleus of Deiters were stimulated indirectly by stimulating the nucleus fastigii. The descending effects of this stimulation are known [18, 21, 26, 29, 30] to be mediated by the medullary reticular formation and nuclei of the vestibular complex. The gigantocellular nucleus and Deiters' vestibular nucleus are relay structures for impulses from the cerebellum [16, 19, 22, 24]. To stimulate the nucleus fastigii a volley of five square pulses was applied (500/sec, 8 msec, esch stimulus 0.1 msec); single stimuli were applied in some experiments. Steel microelectrodes (tip 5–10 μ in diameter) were inserted by means of a stereotaxic apparatus in accordance with Szentagothai's atlas. The position of the electrodes in the brain was verified in sections stained by Nissl's method. In control experiments tetanus toxin inactivated with antitetanus serum was injected into the medullary nuclei. The results were subjected to statistical analysis [10].

EXPERIMENTAL RESULTS AND DISCUSSION

Descending Inhibition of Polysynaptic Reflexes after Injection of Tetanus Toxin into the Gigantocellular Nucleus. Normally (Fig. 1A and B, curve I), descending inhibition of polysynaptic reflexes evoked by stimulation of the nucleus fastigii arises after a fairly long latent period; inhibition is often preceded by very slight transient facilitation. In most cases two maxima of inhibition were observed after intervals of 30–40 and 100–160 msec. The inhibition gradually died away, and by 300 msec the reflexes had returned to their initial value.

After injection of tetanus toxin into the gigantocellular nucleus the latent period of inhibition was significantly ($P < 0.05$) shortened and its depth and duration were increased (Fig. 1A and B, curves II, III). With the course of time these effects increased. The inhibition curve retained its biphasic character only for the first few hours after injection of the toxin; later, e.g., after 24 h, the course of the curve changed: the inhibition began after an even shorter latent period, reached its maximum (95%) quickly, and remained at the same level for a long time.

In five experiments in which inactivated tetanus toxin was injected into the gigantocellular nucleus the depth and intensity of descending inhibition did not increase with time.

Descending Facilitation of Monosynaptic Extensor Reflexes after Injection of Tetanus Toxin into Deiters' Nucleus (Fig. 2). Under normal conditions Fig. 2A and B, curve I) two maxima of descending

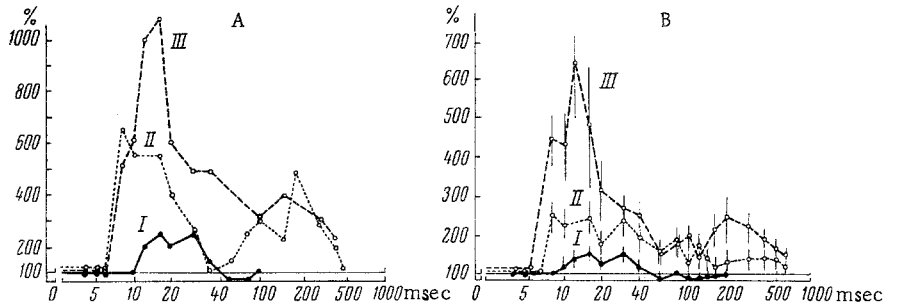

Fig. 2. Suprasegmental facilitation of extensor monosynaptic reflexes induced by stimulation of the nucleus fastigii increased after injection of tetanus toxin into the lateral vestibular nucleus of Deiters. A) Facilitation of extensor monosynaptic reflexes before (I) and 6 (II) and 24 h (III) after injection of tetanus toxin (90 MLD for mice) into Deiters' nucleus (P6–D4–H0). Monosynaptic reflexes recorded from nerve to gastrocnemius muscle. Results of one experiment. B) General curves of suprasegmental facilitation of extensor monosynaptic reflexes plotted from averaged results of 7 experiments (M ± m): I) before, II) 2 h and III) 4 h or more after injection of toxin (90 MLD for mice) into Deiters' nucleus.

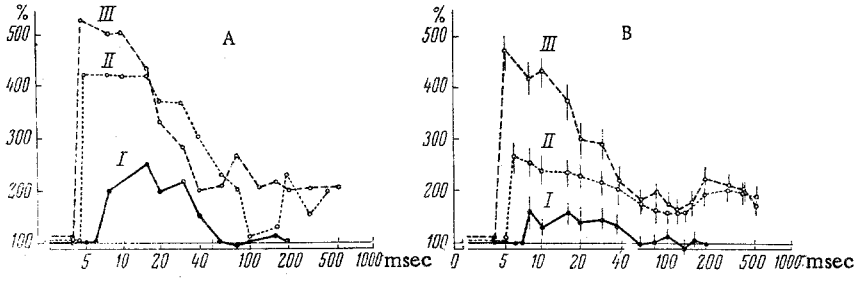

Fig. 3. Segmental facilitation of flexor monosynaptic reflexes produced by stimulation of nucleus fastigii increased after injection of tetanus toxin into nucleus ambiguus. A) Facilitation of flexor monosynaptic reflexes before (I) and 4 (II) and 24 h (III) after injection of tetanus toxin (100 MLD for mice) into nucleus ambiguus (P9–D3–H3). Monosynaptic reflexes recorded from deep peroneal nerve. Results of one experiment. B) General curves of suprasegmental facilitation of flexor monosynaptic reflexes plotted from averaged results of 6 experiments (M ± m): I) before, II) 2 h and III) 4 h or more after injection of tetanus toxin into nucleus ambiguus.

facilitation were observed within the interval 15–30 msec. This is in agreement with data in the literature [25]. The facilitation then decreased and sometimes was replaced by slight inhibition and it terminated by 100–150 msec.

After injection of tetanus toxin into the lateral vestibular nucleus of Deiters (Fig. 2A and B, curves II, III) the latent period of the reflex was shortened and facilitation very considerably (by 5–10 times) increased ($P < 0.01$); with the course of time these effects increased. Facilitation began almost immediately after the end of stimulation and rose sharply to a maximum. This pattern of development of facilitation became particularly marked 24 h after injection of the tetanus toxin (Fig. 2A, curve III). In some experiments the thresholds of the monosynaptic responses fell considerably after injection of the tetanus toxin into Deiters' nucleus and their amplitude increased without any additional conditioning stimulation of the cerebellum. It is an interesting fact that in some cases an increase in the flexor monosynaptic reflexes could also be observed after injection of tetanus toxin into Deiters' nucleus. This fits in with data showing that stimulation of Deiters' nucleus can cause facilitation of flexor as well as of extensor reflexes [20].

In the three experiments in which inactivated tetanus toxin was injected into Deiters' nucleus no changes were found in facilitation.

Descending Facilitation of Flexor Monosynaptic Reflexes after Injection of Tetanus Toxin into Nucleus Ambiguus (Fig. 3). Under normal conditions the curve of descending facilitation of flexor monosynaptic reflexes to stimulation of the rostral and caudal parts of the nucleus fastigii is usually bimodal in character (Fig. 3A and B, curve I). In this respect it resembles the curve of facilitation of the monosynaptic extensor reflexes: the only noticeable differences were a somewhat greater degree of facilitation and a shorter latent period.

After injection of the tetanus toxin into the nucleus ambiguus the degree and duration of facilitation increased significantly ($P < 0.01$) and the latent period was shortened; facilitation continued for 500 msec or more (Fig. 3A and B, curves II and III). It reached its maximum almost immediately and then declined slowly over a long period of time. In three experiments no change in facilitation or in the latent periods of the response were found after injection of inactivated tetanus toxin into the nucleus ambiguus.

The investigations show that after injection of tetanus toxin into the medullary nuclei, the descending inhibitory (gigantocellular nucleus) and facilitatory (nucleus of Deiters, nucleus ambiguus) were sharply intensified. This result conflicts with the reported observations that tetanus toxin has no effect on the medullary reticular formation [23].

The changes produced by tetanus toxin in the descending effects were specific. Considering that some types of postsynaptic [3, 11, 17] and presynaptic inhibition [1, 9] are disturbed by the toxin at the spinal level and that similar inhibition may take place also in the system of the medullary nuclei studied in the present experiment [27, 28], it can be concluded that the effects of tetanus toxin are connected with a disturbance of inhibition in these nuclei.

The results of the present investigation illustrate the role of inhibitory processes in the determination of the temporo-spatial pattern of excitation in the nuclei of the medullary reticular formation.

The considerable increase in the intensity and duration of the discharges ("functional dispatches") arising from the medullary nuclei after injection of tetanus toxin into them is evidence of the formation of powerful excitation generators in these nuclei in connection with the disturbance of their inhibitory mechanisms, as a result of which these nuclei become pathologically augmented "dispatch stations." These unique features of operation of the generator, especially its prolonged activity, suggest that the reverberation of excitation is a mechanism concerned in the activity of the generator.

This investigation thus showed that pathologically augmented "dispatch stations" can be formed in the suprasegmental apparatus. Its results also point to a very important feature of the DS phenomenon, namely that the functional role of its effects is determined by the system in which it is formed.

LITERATURE CITED

1. A. D. Ado, G. V. Burlakov, and Yu. S. Sverdlov, Dokl. Akad. Nauk SSSR, 167, 478 (1966).
2. G. N. Kryzhanovskii, in: Problems in Physiology and Pathology of the Nervous System [in Russian], Moscow (1962), p. 34.
3. G. N. Kryzhanovskii, Tetanus [in Russian], Moscow (1966).
4. G. N. Kryzhanovskii, in: General Neurophysiology and Experimental Pathology of the Nervous System [in Russian], Moscow (1970), p. 43.
5. G. N. Kryzhanovskii, in: Models of Diseases [in Russian], Moscow (1973), p. 120.
6. G. N. Kryzhanovskii, Pat. Fiziol., No. 4, 3 (1973).
7. G. N. Kryzhanovskii and F. D. Sheikhon, Byull. Éksperim. Biol. i Med., No. 11, 9 (1968).
8. G. N. Kryzhanovskii and F. D. Sheikhon, Byull. Éksperim. Biol. i Med., No. 7, 34 (1970).
9. G. N. Kryzhanovskii and F. D. Sheikhon, Exp. Neurol., 38, 110 (1973).
10. E. V. Montsevichyute-Éringene, Pat. Fiziol., No. 4, 71 (1964).
11. Yu. S. Sverdlov, Neirofiziologiya, 1, 25 (1969).
12. F. D. Sheikhon, in: Problems in Physiology and Pathology of the Nervous System [in Russian], Moscow (1966), p. 119.
13. F. D. Sheikhon, G. N. Kryzhanovskii, and S. I. Igon'kina, in: Proceedings of the 11th Congress of the I. P. Pavlov All-Union Physiological Society [in Russian], Vol. 2, Leningrad (1970), p. 56.
14. F. D. Sheikhon, in: Brain and Movement (Abstracts of Proceedings of a Symposium) [in Russian], Erevan (1973), p. 160.
15. F. D. Sheikhon and M. B. Rekhtman, in: Convergence and Synapses [in Russian], Moscow (1973), p. 193.

16. A. Brodal, F. Wallberg, and O. Pompeiano, The Vestibular Nuclei [Russian translation], Moscow–Leningrad (1966).
17. V. B. Brooks, D. R. Curtis, and J. C. Eccles, J. Physiol. (London), 135, 655 (1957).
18. M. B. Carpenter, D. S. Bard, and F. A. Alling, J. Comp. Neurol., 11, 1 (1959).
19. S. Grillner, T. Hongo, and S. Lund, Exp. Brain Res., 10, 94 (1970).
20. M. Ito, M. Udo, N. Mano, et al., Exp. Brain Res., 11, 29 (1970).
21. D. B. Lindsley, L. N. Schreiner, and H. W. Magoun, J. Neurophysiol., 12, 197 (1949).
22. H. W. Magoun, Physiol. Rev., 30, 459 (1950).
23. R. Naquet, H. Regy, and H. Gastaut, J. Physiol. (Paris), 50, 428 (1958).
24. K. Sasaki and T. Tanaka, Jap. J. Physiol., 13, 64 (1963).
25. R. S. Snider, W. S. McCulloch, and H. W. Magoun, J. Neurophysiol., 5, 325 (1949).
26. J. M. Sprague and W. W. Chambers, Am. J. Physiol., 176, 52 (1954).
27. A. K. Tabécis and T. Ishikawa, Pflüg. Arch. ges. Physiol., 338, 273 (1973).
28. A. K. Tabécis and A. D. L. Maria, Brain Res., 40, 373 (1972).
29. F. O. Wallberg, O. Pompeiano, A. Brodal, et al., J. Comp. Neurol., 118, 49 (1962).
30. R. M. Wylie, Exp. Brain Res., 12, 128 (1971).