INHIBITORY AND FACILITATORY EFFECTS FROM THE MEDULLA IN EXPERIMENTAL LOCAL TETANUS

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UDC 616.981.551-092.9-07 : 616.831.8-009.81

After administration of tetanus toxin, descending facilitatory effects are strengthened while inhibitory effects are weakened. At the height of development of local tetanus, stimulation of facilitatory structures causes excitation (evoked activity in the muscles), while during stimulation of inhibitory nuclei not only does the inhibitory effect disappear, but equally high polysynaptic activity develops.

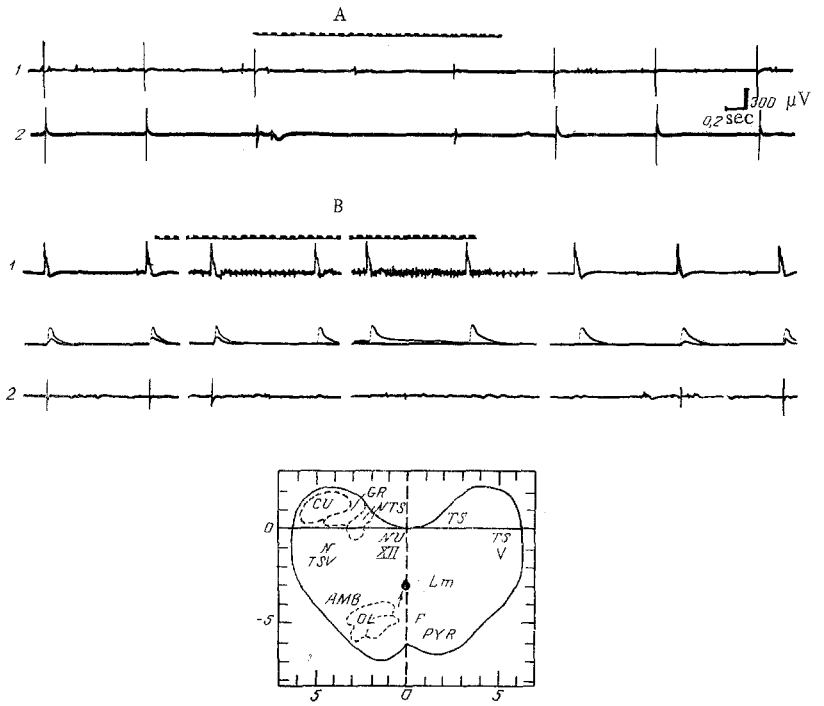

Fig. 1. Effect of stimulation of nuclei of the median raphe of the medulla under normal conditions (A) and in local tetanus (B). Significance of curves: reflex responses of lateral head of gastrocnemius muscle to stimulation of nerve to medial head in left (1) and right (2) hind limbs; B) mean curves obtained by recording electrical activity with an integrator; broken line, marker of brain stimulation. Localization of electrodes P9DOH-3 (interpolated on the basis of the paper by Taber and co-workers [15]) indicated on diagram by arrow. 3rd day after injection of toxin: case in which increased background activity in muscles of limb receiving injection of tetanus toxin was absent chosen specially to obtain a clearer picture of reflex responses.

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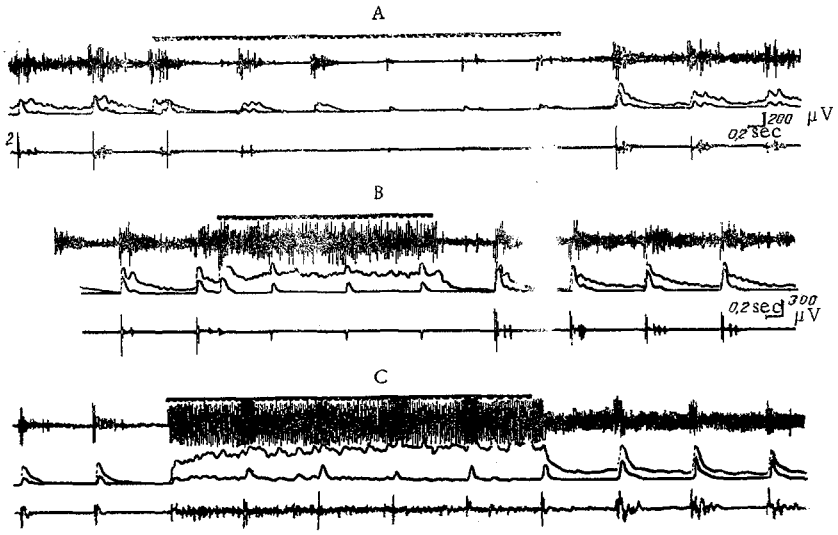
TABLE 1. Effects of Stimulation of Facilitatory and Inhibitory Structures of the Medulla at Various Periods of Development of Local Tetanus

Brain structures stimulated	2nd day				3rd day				4th-7th day			
	number of experiments	inhibition present	inhibition absent	appearance of activity	number of experiments	inhibition present	inhibition absent	appearance of activity	number of experiments	inhibition present	inhibition absent	appearance of activity
Inhibitory nuclei	50	28 *	12	10	98	10 *	18	70	10	0	3	7
Facilitatory nuclei	number of experiments	facilitation and appearance of activity		no effect	number of experiments	facilitation and appearance of activity		no effect	number of experiments		facilitation and appearance of activity	no effect
	25	19		6	78	77		1	10		10	0

*Inhibitory effects weakened.



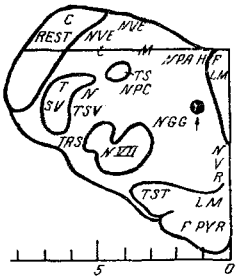


Fig. 2. Effects of stimulation of gigantocellular nucleus in local tetanus. A) 2, B) 4, C) 7 days after injection of toxin. Significance of curves: reflex responses of left (1) and right (2) semitendinosus muscles to stimulation of peroneal nerve; mean curves obtained by recording electrical activity with an integrator; broken line, marker of brain stimulation; localization of electrodes (P7D1H-3) marked on diagram by arrow.

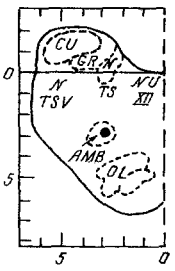


Fig. 3. Effects of stimulation of nucleus ambiguus in local tetanus (3rd day after injection of toxin). Significance of curves: reflex responses of lateral head of gastrocnemius muscle to stimulation of nerve to medial head of left (1) and right (2) hind limbs; mean curves obtained by recording electrical activity with an integrator; broken line, marker of brain stimulation; localization of electrodes (P9D3.5H-3) marked on diagram by arrow.

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Tetanus toxin disturbs various types of segmental postsynaptic inhibition of motoneurons [4, 5, 9]. The effect of tetanus toxin on descending inhibition has received much less study [6, 10]. Results have been obtained indicating that the paroxysmal activity of muscles is increased in animals with local tetanus in response to stimulation of the mesencephalic reticular formation [1].

The object of the present investigation was to study the effect of inhibitory and facilitatory structures of the medulla on activity of the spinal reflex apparatus in local tetanus.

EXPERIMENTAL METHOD

Experiments were carried out on cats lightly anesthetized with nembutal and chloralose (10 and 12 mg/kg respectively, intraperitoneally). Structures of the medulla were stimulated through unipolar and bipolar (interelectrode distance 100-400 μ) steel microelectrodes (diameter of tip 5-10 μ) with square pulses (0.5-5 V, 60-100 Hz, 0.1 msec). The microelectrodes were introduced through the cerebellum in accordance with the coordinates of Szentagothai's atlas. Reflex responses of muscle antagonists of the same and of different joints (gastrocnemius, semitendinosus, quadriceps, tibialis anterior) were recorded by means of a "Disa" electromyograph. The position of the microelectrodes was verified macroscopically (after removal of the cerebellum) and microscopically (in histological sections) after the experiment.

Local tetanus was produced by injection of the toxin (1/200-1/50 MLD) at several points into the left gastrocnemius muscle and the posterior group of muscles of the left thigh. Earlier work in this laboratory [3] showed that after injections into these muscles the toxin travels along the sciatic nerve to enter the anterior horns of the corresponding segments of the spinal cord on the side of injection via the ventral roots.

EXPERIMENTAL RESULTS

In experiments on healthy animals facilitatory effects were obtained in response to stimulation of the parvocellular nucleus, the nucleus ambiguus, and nuclei of the vestibular complex. Inhibitory effects were produced by stimulation of the gigantocellular nucleus and ventral reticular nucleus and also by stimulation of a comparatively limited area located outside the reticular formation in the midline, in the region of the median raphe, described by some authors as the nucleus of the median raphe [15]. Stimulation of the inhibitory zone depressed reflex activity of the flexors and extensors of both limbs (Fig. 1, A).

During development of local tetanus the effects of stimulation of the inhibitory zones underwent characteristic changes. Two days after injection of the toxin, when the clinical manifestations of local tetanus were comparatively slight, descending inhibition was already distinctly weakened on the affected side, and after 3 days, stimulation of the inhibitory zones caused weakening of reflex activity only in rare cases, the inhibition being almost completely abolished in most cases (Table 1; Figs. 1, B and 2, A, B). At the height of development of local tetanus (4-7 days) complete abolition of the inhibitory effects was observed. In the late stages of action of the toxin if this had spread to the opposite side, similar changes were observed on

this side also (Fig. 2, C). A striking feature of the phenomena investigated was that as the toxic manifestations developed not only were the inhibitory effects abolished, but they were replaced by polysynaptic activity arising in response to stimulation of the inhibitory nuclei. This effect increased parallel with the disturbance of inhibition and in the late stages was particularly well marked (Table 1; Fig. 2, B, C).

In response to stimulation of the facilitatory zones in animals with local tetanus, besides an increase in the reflex responses, which was more marked on the side of injection of the toxin, considerable polysynaptic activity appeared (Table 1, Fig. 3). The intensity of the later increased with the development of the toxic manifestations, and at the height of local tetanus stimulation of the facilitatory zones alone evoked a powerful burst of electrical activity in the muscles of the affected limb. The threshold of these effects was lowered to almost one-tenth of the threshold for facilitatory responses in healthy animals. This accounts for the difficulty in distinguishing between facilitatory and direct excitatory effects when the facilitatory nuclei of the reticular formation are stimulated during local tetanus. In some experiments a "rebound phenomenon" could be observed: disappearance of electrical activity immediately on stopping stimulation. This phenomenon was also observed in cases of stimulation of inhibitory nuclei.

The whole of this pattern of the effects produced by stimulation of the inhibitory and facilitatory zones of the medulla was also reproduced under conditions of decerebration.

It can thus be concluded from the results obtained that after injection of tetanus toxin not only segmental postsynaptic inhibition, but also some types of descending inhibition are disturbed. It may therefore be supposed that types of segmental and suprasegmental inhibition which are abolished by tetanus toxin are identical in nature. The fact that when the same point of the inhibitory nuclei was stimulated the inhibitory effect was disturbed only on the side of injection of the toxin and persisted on the opposite side (except in the late stage of local tetanus) is evidence that this result was due to the action of tetanus toxin at the spinal level and that inhibitory mechanisms were disturbed in the spinal reflex apparatus.

The reason for the replacement of the descending inhibitory effect by an excitatory effect in tetanus is not yet clear. It may be connected with the fact the inhibitory nuclei are in fact not purely inhibitory, for they may contain elements producing facilitation [2, 7, 8]. This view is supported by findings indicating the presence of "mixed" effects stimulation of suprasegmental structures [7, 8, 11, 13, 14, 16]. When inhibition is disturbed, excitatory effects of mixed volleys may become apparent. Under normal conditions we have also observed facilitatory and excitatory effects of stimulating certain zones of the inhibitory nuclei. Such an effect was observed in response to stimulation with a current of considerable strength. With this possibility in mind, we attempted to localize the stimulation more accurately by using a weaker current and bipolar electrodes with minimal interelectrode distance (not exceeding 100 μ). Under these conditions consistent experimental results were obtained and in every case when tetanus had developed activity appeared in the muscles in response to stimulation of the inhibitory zones.

Another possible explanation of the observed phenomenon is that when neurons of the inhibitory zone are stimulated excitation passes along the descending pathways not only to inhibitory, but also to excitatory interneurons of the spinal cord, or in other words, the original volley from the inhibitory zones is identical, but at the spinal level it goes to two different destinations. Under normal conditions the excitatory effects are suppressed by the inhibitory (possibly because of different quantitative relationships between the pathways, etc.), but when inhibitory mechanisms in the spinal cord are blocked, the latent excitatory effects become manifest. Similar relationships are evidently found in the case of inhibitory volleys at the segmental level also [4, 12]. The mixed effects of stimulation of suprasegmental inhibitory structures mentioned above [7, 8, 11, 13, 14, 16] may be explained from this point of view also.

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