EFFECT OF TRIMETHINE ON SPINAL REFLEX FACILITATION AND INHIBITION FROM STIMULATION OF THE BRAIN-STEM RETICULAR FORMATION

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The actions of anticonvulsants are generally examined in models of convulsive states. At the same time, an understanding of the pharmacodynamics of these substances is likely to be furthered by an examination of their effects on the course of elementary nerve processes, which would include facilitating and inhibitory mechanisms connected with the control of movements and playing an important part during the period of convulsive activity.

An investigation of the effect of one anticonvulsant, trimethine, and its antagonist, corazol, on facilitation and inhibition of the patellar reflex by stimulation of the caudal region of the reticular formation in the brain stem. Structures in this part of the brain play a special role in coordination of the motor act, and, as is well know, are concerned in the transmission of most extrapyramidal and some pyramidal impulses [5].

METHOD

There were in all 33 experiments, 20 on anesthetized (urethane 1g/kg intravenously), 10 on decerebrate and 3 on spinal cats. The index of motor activity was the mechanographically recorded patellar reflex. Electrical stimulation of the brain stem (10-300 impulses per sec, impulse length 1 msec, voltage 0.25-5.0 V) was effected through 3 or 4 unipolar electrodes in different sections of the floor of the fourth ventricle, the actual area stimulated being determined histologically later [1,4]. The occurrence of facilitation or inhibition was determined from comparison of the magnitude of five reflex contractions during the period of brain stem stimulation.

The substances under examination, trimethine and corazol, were injected intravenously in doses of 50-400 mg/kg and 10-20 mg/kg, respectively.

RESULTS

Facilitation of the patellar reflex was observed when various brain-stem structures, differing in function, were being stimulated (in all,56 points were examined). Facilitation was seen most constantly when the reticular nuclei of the pons, the nuclei of the vestibular complex,or the small-cell reticular nucleus were being stimulated. The optimum frequencies producing facilitation were between 100 and 150 c/s, irrespective of the nature of the formation stimulated. Higher rates of stimulation led to the development of a tonic component in the facilitatory reaction, this being particularly noticeable in decerebrate animals. Mixed forms of response could occasionally be noted from the same point in the brain; when the rate or strength of stimulation was increased, there was inhibition of reflex movements in place of the former facilitation. This phenomenon was probably due to looping of the current to structures having inhibitory functions adjoining the activated zone.

Without producing any significant change in the amplitude of the patellar reflex, trimethine definitely suppressed supraspinal facilitation, irrespective of the area stimulated, and equally in anesthetized and decerebrate animals. The elements most sensitive to trimethine in the facilitatory reaction were the tonic components, seen as increasing extension during stimulation or transient clonus of the flexors of the thigh after stimulation ended. This type of tonic facilitation was very easily abolished by even small doses (50 mg/kg) of trimethine (Fig. 1B). This is

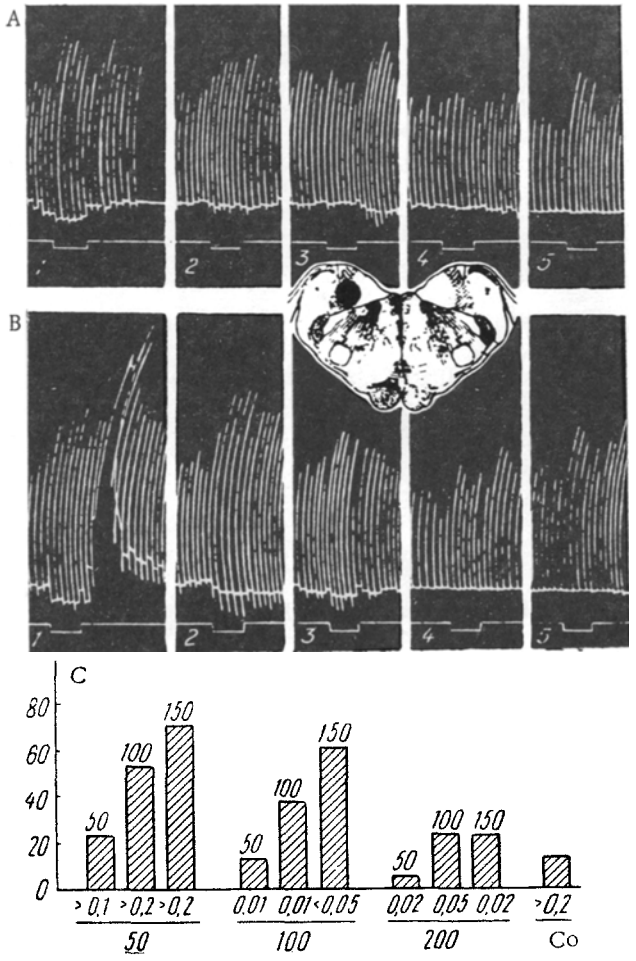

Fig. 1. Effect of trimethine on facilitation of patellar reflex during stimulation of nuclei of vestibular complex A and B. Data from one experiment in which facilitating effects from stimulation at rates of 100 and 150 per sec, respectively, were recorded: 1) normal state; 2-4) after injection of trimethine in doses of 50, 100, and 200 mg/kg, respectively; 5) after injection of corazol following trimethine. Diagram – position of stimulating electrode. C – general changes in descending facilitation, associated with stimulation of nuclei of vestibular complex, produced by increasing doses of trimethine. Columns – mean value of facilitary response with various stimulation frequencies (numbers over columns – percentages of initial facilitation). First row of numbers below columns – index of reliability of differences (P); second row – dose of trimethine (mg/kg). Average value of facilitation with different stimulation rates after injection of corazol – Co.

consistent with the already-observed power of trimethine to abolish, first of all, the extensor component of the tonic phase of electroshock convulsions [9,10].

Small doses did not produce any essential change in the facilitation of the reflex during the actual period of brain-stem stimulation. The processed results (Fig. 2) show that the reductions or increases in the responses from certain structures, sometimes seen after the injection of trimethine, 50 mg/kg, were not significant. Distinct, statistically significant depression of descending facilitatory effects was obtained with large doses (100-200 mg/kg), equivalent to effective anticonvulsant doses [17]. The effect did not become evident immediately (maximum 10-15 min after injection); there was depression, even to the point of complete suppression of the facilitating effect, and sometimes (in 30% of cases) reversal of the reaction to slight inhibition, and the effect lasted for 1-1.5 h. Increase of the dose to 400 mg/kg had no appreciable additional effect.

Supraspinal facilitation was most rapidly and easily attenuated when stimulation was effected at rates just below or above optimum for the particular structure. This is illustrated in Fig. 1. The optimum rate of stimulation for the production of facilitating effects from the nuclei of the vestibular complex was 150 c/s. The trimethine effect was less when the brain stem was stimulated at this rate than when the stimulation frequency was 100 c/s, despite the fact that in some cases, as, for example, in the experiment shown in Fig. 1, A and B, the initial values of facilitation were almost the same for different stimulation frequencies. This same difference could also be observed in the combined results for several experiments (see Fig. 1C). Another important feature, seen in the kymograms of Fig. 1, is the prolonged (circ. 15 sec) after facilitation of reflex movements when stimulation had ended. This was quite resistant to trimethine, and was probably due to hormonal adrenaline, mobilized from the suprarenal glands [16].

It will be evident from Fig. 2 that the effect of trimethine on facilitation did not depend on the location of the stimulating electrode. The responses of structures with direct reticulospinal projections (caudal reticular nucleus of pons, small-cell reticular nucleus) [3], and the responses of cerebral nerve nuclei, impulse activity from which reaches the spinal cord indirectly, and after switching to effector groups of neurons in the medial part of the brain stem [14,15,18], were suppressed to about the same degree. This suggests that trimethine makes the conduction of impulses difficult through elements of the terminal pathway, the common pathway for the transmission of facilitating effects from different sources. The systems of propriospinal neurons, which are indispensable for realization of pyramidal, vestibulospinal and reticulospinal effects [12,19], may provide this common pathway. The actual mechanism of the trimethine effect on supraspinal facilitation would appear to consist of two elements, namely a reduction of the tendency to

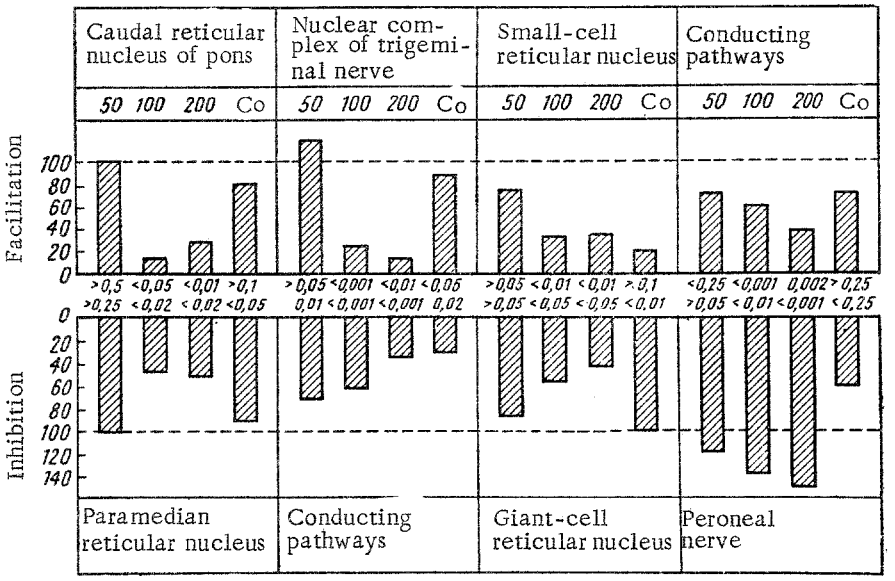

Fig. 2. Trimethine-induced changes in facilitation and inhibition of patellar reflex associated with stimulation of various brain-stem structures. Columns – average reaction values for different rates of stimulation (percentages of initial values) and different doses of trimethine (upper row of figures) and corazol (Co). Middle row of figures – reliability of differences (P).

repeated discharge in the cells of the centrifugal propriospinal systems and interference with postsynaptic processes of facilitation actually in the motoneurons resulting from stabilization of the cell membranes [20].

Facilitation of the patellar reflex by direct stimulation of descending tracts in the brain stem or, in the case of spinal animals, in the region of the upper cervical segments was, like the spinal convulsions in Esplin's experiments [7], more resistant to trimethine. The reason for this may be that the trans-synaptic activation of conducting pathways resulting from stimulation of their nuclear formations was less widespread and less effective than their activation by direct stimulation.

Corazol intensified suprasegmental facilitation associated with stimulation at different points in most cases. Exceptional sites in this respect were the ventral and small-cell reticular nuclei, as the facilitation associated with stimulation of these formations was, as Bondarev [2] has also observed, often reduced by the analeptic. Corazol given after trimethine produced partial restoration of facilitation in many cases, but sometimes had no appreciable effect (see Figs. 1 and 2). The tonic component of the reaction of facilitation was most readily restored. The trimethine effect could not be abolished completely, and results generally merely indicated a trend towards restoration, as the animal usually developed motor activity when the corazol dosage was increased. At the same time, the depression of responses from the ventral and small-cell reticular nuclei produced by trimethine became even more pronounced after the injection of corazol, which meant that, in this particular situation, the two substances, so different from one another, acted as synergists.

Inhibition of the spinal reflex developed most regularly when the giant-cell reticular nucleus was stimulated. In its characteristics, the inhibition had much in common with the inhibitory responses from other structures (in all 44 points were examined). As in the case of facilitation, the most effective frequencies lay between 100 and 150 c/s.

Trimethine interfered in quite a distinct way with the course of suprasegmental inhibition. The effect, only slight with small doses (50 mg/kg), was much more definite with doses of 100-200 mg/kg. The inhibition of the reflex, associated with stimulation of a structure at the rate optimum for that particular formation, was particularly resistant to trimethine (Fig. 3). Comparison of its effects on inhibitory reactions of various origins indicated that they were suppressed in much the same way, at whatever point the midbrain was stimulated (see Fig. 2). The responses of the giant-cell reticular nucleus, with direct reticulospinal projections, and those of the paramedian reticular nucleus, impulses from which reach the spinal cord after switching to efferent formations in the brain stem [3], were reduced in equal degree. Unlike facilitation, inhibition was quite effectively abolished by direct

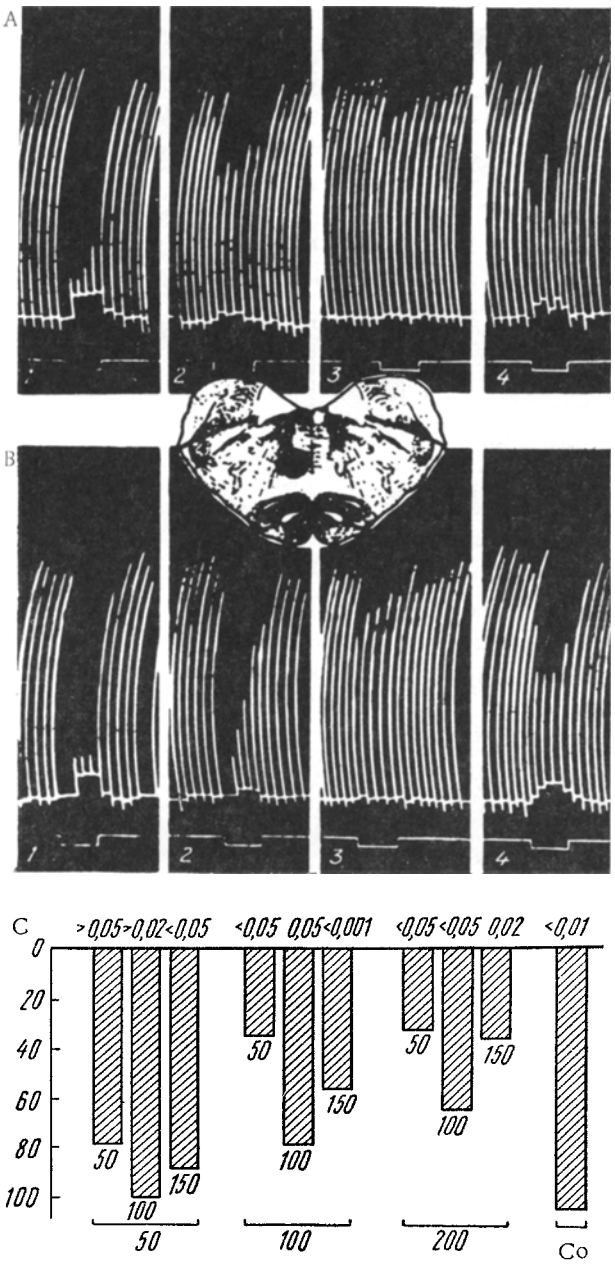

Fig. 3. Reduction of inhibitory effect from stimulation of giant-cell reticular nucleus by trimethine.

stimulation of the conducting pathways. The depression of inhibitory reactions by trimethine in doses of 100 mg/kg was statistically significant in all cases.

Inhibitory reactions, irrespective of origin, were intensified by corazol. Injected after trimethine, it had an antagonistic effect in most instances, resotring inhibition. This effect was absent only when descending tracts were stimulated.

The power of trimethine to reduce supraspinal inhibition would appear to be based largely on the same neurophysiological mechanisms as its action on facilitation, as the same functional units in the bulbo-spinal correlative system transmit effects of different kinds to the segmental apparatus [13]. The more complex organization of inhibitory (as compared with facilitatory) pathways, resulting from the inclusion of a supplementary specialized inhibitory intercalary neuron would appear to account for the absence of any difference in the effects of trimethine on the inhibitions associated with stimulation of nuclear formations and descending tracts, respectively.

The electrophysiological features of the actual postsynaptic process, underlying motoneuron facilitation, are probably responsible for its greater sensitivity (in comparison with inhibition) to trimethine. This difference is best seen by comparison of the degrees to which facilitatory and inhibitory reactions are suppressed from individual brain-stem structures (see Fig. 2). Further evidence of this is provided by the fact that, when stimulation of any formation produced mixed effects, facilitation with some stimulation parameters and inhibition with others, trimethine (100 mg/kg) produced distinct depression of facilitating effects during the first 5-8 min after its injection, when inhibitory effects were unchanged or might even be intensified. Only later, or when dose was increased, was inhibition reduced. The dissimilar resistances of supraspinal facilitation and inhibition to trimethine was apparently responsible for a shift towards greater inhibition in the equilibrium between the two systems controlling movement.

The reversal of facilitation and inhibition, seen in a number of the trimethine experiments, can also be explained from the same standpoint. There is, however, yet another possible explanation. One of the reasons for the suprasegmental facilitation of monosynaptic reflexes may be primary functional depression of intermediate cells in some segmental inhibitory pathways [6,11]. The depressant effects spread to intercalary neurons in inhibitory pathways from afferent Ib and II groups. If such a mechanism exists, trimethine would, a priori, by interfering with transmission over descending facilitatory pathways, free segmental inhibitory apparatuses from retarding control, and thus intensify inhibition of reflex movements. In pursuance of this argument, an examination was made of the effect of trimethine on postsynaptic conjugate inhibition of the patellar reflex, associated with stimulation of the superficial branch of the ipselateral peroneal nerve. The assumptions proved correct, and this form of inhibition, unlike supraspinal inhibitory reactions, was regularly intensified by trimethine. Even with small doses, the intensification of inhibition was very close to being statistically significant, and with large doses it was completely so (see Fig. 2). An interesting point is that the functioning of intercalary cells in the inhibitory pathway from group IA

afferents, freed from supraspinal control [6,11], was, according to observations by Esplin and Kurto [8], unchanged by the injection of trimethine. Intensification of reciprocal inhibition, produced by trimethine, was removed by corazol, despite the fact that the analeptic, itself, always intensified this form of inhibition.

Trimethine thus reduced facilitation and inhibition of the patellar reflex induced by stimulation of various structures in the reticular formation of the brain stem. Its effect was greater on facilitating effects. It can probably be accounted for by blocking of impulse transmission through systems of propriospinal neurons, and was associated with activation of polyneuronal segmental inhibitory pathways.

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