THE INFLUENCE OF NOVOCAINE ON PESSIMAL INHIBITION IN VARIOUS LINKS OF THE REFLEX ARC

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Novocaine has in recent years been shown to possess a wide spectrum of action. Besides the generally known properties of anesthesia, novocaine shows the following effects upon resorptive action: depression of transmission of excitation in the central nervous system [2-7], in autonomic ganglia [1, 9, 10, 13] and partially in neuro-muscular synapses [13-16], as well as in the region of m-choline receptors [11].

In the present investigation an attempt was made to discover certain aspects of the mechanism of novocaine action within the framework of studies on its influence on processes of pessimal inhibition in different links of the reflex arc.

The influence of novocaine on neuro-muscular transmission. Experiments were carried out on decerebrate cats. Records of the contractions of the gastrocnemius muscle were made under semi-isometric conditions. The peripheral segment of the tibial nerve was stimulated by square-pulse stimuli each of 0.5 millisecond duration. The frequency of stimulation was varied from 0.5 up to 300 cps. Stimulation at each frequency was continued for 10 seconds. Novocaine was given intravenously.

Novocaine in doses 2.5-5 mg/kg did not exert any appreciable effect on neuro-muscular transmission. The amplitude of the muscular contractions on stimulation at frequencies of 0.5-10-20 and 50 cps increased slightly or remained unchanged when 10-15 mg/kg novocaine had been administered. At the same time a more rapid decline of the tetanic curve at frequencies of 80-200 cps was observed. Primary twitching at these frequencies was somewhat more pronounced than in the normal. In doses of 25 mg/kg novocaine led to a definite decrease in the amplitude of the myogram at all frequencies of stimulation (Fig. 1). The pessimal reaction began to be apparent at 50 cps and became most definite at 80-200 cps. Restoration began fairly rapidly and after 12-20 minutes was already practically complete. The maximal effect of the substance was attained in the first 5 minutes following its injection.

On repeated injection of novocaine its effect was less marked than that achieved after the first injection.

There are references in the literature to the fact that novocaine can diminish acetylcholine production [13]. With this in mind, experiments were carried out in which the effect of proserine* on the activity of novocaine was examined. Proserine was used in doses of 20-40 kg. Under these conditions an increase in the amplitude of single contractions and a considerable shift of the pessimum toward the lower frequencies were observed. The primary twitch of the muscle was somewhat increased with the range of frequencies from 50-200 cps. Administration of novocaine against this background (25 mg/kg) lowered the amplitude of muscular contractions to a considerable extent. Pessimal reaction could already be seen at a frequency of 50 cps.

* Russian trade name.

The action of novocaine passed after 35-40 minutes, whereas changes in neuro-muscular transmission associated with the effect of proserine persisted. This interrelation could also be observed when smaller doses of of both the substances were used. Thus, the synergism of proserine and novocaine was observed when proserine was used in such doses (1-5 γ/kg) which by themselves did not alter neuro-muscular transmission appreciably.

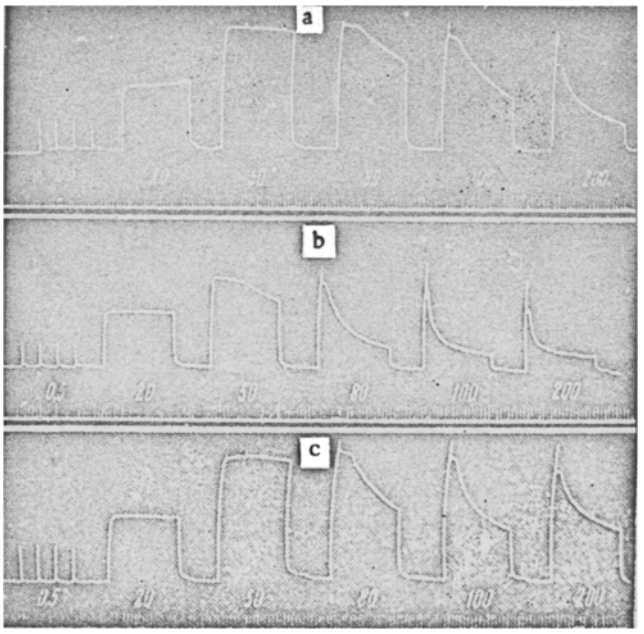

Fig. 1. The effect of novocaine on neuro-muscular transmission. a) Before administration of the substance; b) 2 minutes after injection of 25 mg/kg novocaine; c) after 15 minutes. Frequency of stimulation of the tibial nerve is marked by figures (in cps).

The effect of novocaine on autonomic ganglia.

These experiments were carried out mainly on the superior cervical ganglion of decerebrate cats. Contractions of the nictitating membrane were recorded upon stimulation of the preganglionic trunk by square-pulse stimuli at various frequencies. The technique used has been described earlier [12].

The minimal dose of novocaine which exerted an influence on the level of pessimal inhibition in the ganglion was equal to 1-2 mg/kg. The effect was observed particularly clearly when novocaine was used in doses of 5-10 mg/kg (Fig. 2) and higher. In Fig. 2 the initial pessimal frequency was 200 cps; relaxation of the membrane took place gradually. Following administration of novocaine (10 mg/kg) the pessimum occurred at a frequency of 80 cps and the decline of the curve was very steep. Change of the pessimal frequency to the optimal (10 cps) led to restoration of the curve. Such a dependence of the effect on the frequency indicates that the observed inhibition is pessimal. It is characteristic for novocaine that there is usually a change in the reaction to optimal frequency of stimulation too, following its administration. The same figure shows that the height of the mechanogram is decreased at the frequency of 10 cps. This means that the excitability of the ganglion cells is lowered under the influence of novocaine. The possibility is not excluded that a definite role may be played by a reduction of acetylcholine production [13]. Doses of 5-10 mg/kg and higher are associated with a shift of the pessimum toward lower frequencies which occurs parallelly with diminution of the excitability of the ganglion cells. It is possible to observe changes elicited by pessimal inhibition without appreciable lowering of ganglion cell excitability by using novocaine in threshold and near-threshold doses.

The duration of novocaine action is not long. It is usually of the order of 20-30 minutes.

Confirmation of the ganglionic action of novocaine was obtained in experiments with recording of biopotentials from the postganglionic fibers. The preganglionic sympathetic trunk was stimulated at various frequencies. It was shown in these experiments that novocaine decreased the amplitude of the biopotentials and shortened the time during which they could be reproduced.

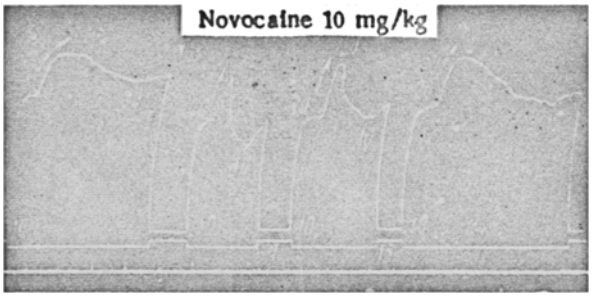

Fig. 2. The effect of novocaine on the lability of the superior cervical ganglion.
Figures indicate the frequency of stimulation of the preganglionic trunk in cps. The gradual transition from lower to higher frequencies is marked by arrows; time marker (30 seconds).

The effect of proserine on the action of novocaine was also studied experimentally in a way similar to that used in the experiments on neuro-muscular transmission. Proserine was used in doses of 20-50 γ/kg and higher. There was no noticeable change in ganglionic transmission of impulses when proserine alone was used. The action of novocaine against the background of proserine (20-30 γ/kg) was somewhat enhanced. Duration of the effect was practically unaltered.

Effect of novocaine on spinal reflexes.

The experiments were performed on lumbar cats. The spinal cord was transected at the level of the lower thoracic vertebrae. Reflex contractions of the semitendinosus muscle were recorded under semi-isometric conditions. The central segment of the fibular nerve (of the same limb) was stimulated by square-pulse stimuli with a duration of 0.1-0.5 millisecond. Stimulation at each frequency was continued for 10 seconds. The intervals between these were no less than 25 seconds, the intervals between each series being 7-10 minutes. Frequencies from 0.5 to 100 cps were used. Novocaine was given intravenously.

Novocaine in doses of 5-10 mg/kg and higher lowered the amplitude of muscular contractions at all frequencies of stimulation of the nerve trunk. Particularly definite changes occurred at the frequency of 0.5 cps. In this case administration of novocaine (12.5-25 mg/kg) was followed by decrease in the height of the mechanogram accompanied by a more rapid relaxation of the muscle. The character of the pessimal reaction, observed as a decline in the tetanic curve, did not change at higher frequencies of stimulation which was evidently connected with enhanced change in the central link of the reflex arc. As recovery from the action of novocaine proceeded there was some facilitation (as compared with the initial) of the reflex transmission of excitation.

Repeated injection of novocaine produced a less marked effect.

In order to investigate the influence of novocaine on pessimal inhibition in the spinal cord, a series of experiments was carried out in which biopotentials were recorded from the deep (motor) branch of the tibial nerve. The more superficial (sensory) part of the same nerve was stimulated by square-pulse stimuli of various frequencies and duration. In these experiments novocaine reduced the amplitude of the potentials. The ability of the cord to reproduce biopotentials over a certain period of time was altered, with shortening of this

period of time. Transformation of the rhythm after administration of novocaine occurred considerably sooner and was more pronounced than before administration of the substance (Fig. 3).

The data obtained indicate that novocaine favors the development of pessimal inhibition in the reflex centers of the spinal cord, sympathetic ganglia and neuro-muscular junctions. Sympathetic ganglia and spinal cord (lumbar segments) are more sensitive to novocaine than neuro-muscular junctions.

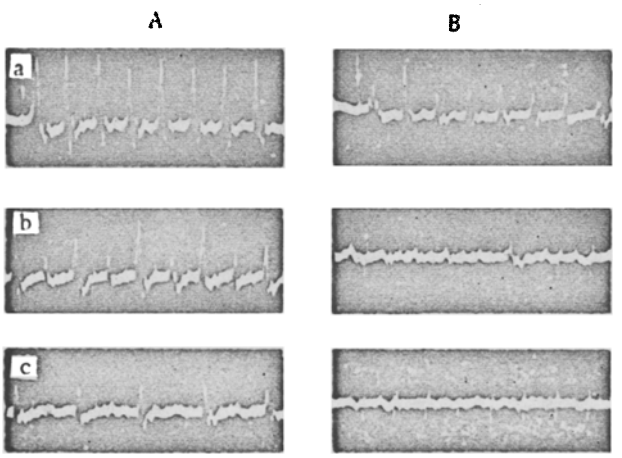

Fig. 3. Effect of novocaine on the lability of spinal centers. Biopotentials before (A) and after (B) administration of 15 mg/kg novocaine.
a) Beginning of stimulation (shown by arrow); b) 5th second after beginning of stimulation; c) 10th second. Biopotentials led off from the motor part of the tibial nerve with electric stimulation of the sensory branch of the same nerve. Frequency of stimulation – 40 cps. Duration of each stimulus – 0.1 millisecond. Short vertical lines – stimulus artifacts.

Attention should be drawn to the fact that when novocaine is combined with proserine the depressing effect of the former with respect to neuro-muscular and ganglionic transmission is not only not weakened but even enhanced to a certain extent. These observations do not agree with the fairly widely held view that the blocking effect of novocaine is caused by its ability to depress acetylcholine synthesis [14 and others]. This view is based on data obtained by Harvey [13] on the superior cervical ganglion. He succeeded in noting that novocaine diminished acetylcholine production connected with stimulation of the preganglionic trunk. However, it was shown in the same work that novocaine diminished the ganglion and skeletal muscle reaction to acetylcholine administered intra-arterially. There is a fairly large number of similar investigations applied to striated muscle [14]. Under such experimental conditions the influence of novocaine on acetylcholine synthesis certainly cannot be the cause of the absence of reaction to acetylcholine. The possibility of alteration in cholinesterase activity is also excluded since in experiments on the superior cervical ganglion the latter was perfused with a solution containing eserine. All this suggests that novocaine exerts a direct influence on synaptic formations also.

Comparison of our data with observations made by Kaverina and Khayutin (1954) draws attention to the considerable difference in the doses of novocaine needed to inhibit the spinal cord. Thus, according to Kaverina and Khayutin, novocaine in doses of 5-7 mg/kg caused considerable inhibition of the flexor reflex in the cat hind limb and blocked it completely in the dose of 16.5 mg/kg. We did not succeed in obtaining similar results. Even in the dose of 25 mg/kg novocaine produced a relatively slight inhibiting effect. A series of control experiments established that such discrepancies were connected with different experimental

conditions. One such difference lay in the fact that our experiments were performed on lumbar cats without any anesthesia while Kaverina and Khayutin tested novocaine on animals under urethane anesthesia (0.5 to 1 g/kg). And urethane is known to inhibit reflex activity of the cord to a significant extent. Against such a background novocaine does indeed block transmission of excitation when given in doses cited by Kaverina and Khayutin. The discrepancy between our data and those reported by Kaverina and Khayutin are thus explained by differences in the functional state of the spinal centers in the experimental animals. As has been shown in the present investigation, considerably smaller doses of novocaine are required to inhibit the reflex activity of the spinal cord in cats under urethane narcosis than in experiments in which no narcosis is used.

SUMMARY

The mechanism of the action of novocaine was studied experimentally. It was demonstrated that in resorptive action of novocaine it increases the pessimal inhibition in the reflex centers of the spinal cord the vegetative ganglia and the neuro -muscular apparatus. Experiments were performed according to the teaching of Vedensky on the functional mobility of the excitable formations.

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