COMPARATIVE ACTION OF ETHER AND CURARIMIMETICS ON THE NEUROMUSCULAR APPARATUS OF WARM-BLOODED ANIMALS IN A CHRONIC EXPERIMENT

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(Received July 2, 1955. Presented by Academician A. D. Speransky)

Much data on the action of ether on the neuromuscular apparatus of the vertebrates has accumulated in the literature, especially recently [7, 9, 10, 11, 14, 15, 17]. However, the nature and mechanism of this action are still unclear in many respects, and data regarding changes in the individual parameters are contradictory [1, 7, 10]. Investigations with the recording of the mechanical effect of the muscle were carried out in acute experiments and sometimes on isolated frog preparations.

We investigated the effect of ether narcosis on the neuro-muscular apparatus of the warm-blooded animal under chronic experimental conditions and against a background of the action of curarimimetics (diplatsin).

EXPERIMENTAL METHODS

Rabbits with an incompletely isolated skeletal muscle were taken for investigation [3]. 56 experiments were carried out on 10 animals, 30 of them with ether narcosis, the rest serving as controls. The narcosis lasted from 30 minutes to 1½ hours. The narcotic state was determined by the disappearance of the pupillary reflex. The action of diplatsin was tested in 10 experiments on 5 rabbits; 0.2% diplatsin solution was administered into the vein of the ear, the total dose equalling 1-1.2 mg/kg. At this dose the decreased irritability and the diminished muscular contraction are well evidenced.

Fig. 1. The action of ether narcosis on refractoriness and exaltation.
a) Before anesthesia; b) 30 minutes after disappearance of the pupillary reflex;
c) 10 minutes after the end of anesthesia.
Numbers of the test groups are designated by numerals.

The following indicators were determined: strength curve – duration, threshold of rhythmic stimulation, contraction in response to rhythmic and solitary rectangular signals of varied strength and duration, dynamics of

irritability after a single stimulus and lability. The measurements were carried out every 10-15 minutes throughout the experiment. When determining all the indicators (except the thresholds) the muscular contractions were recorded on the ribbon of a chymograph. The stimulating electrode was fastened on the cuffed motor nerve, the indifferent electrode was placed on the back. The lability was investigated by means of rhythmic stimulation with rectangular signals 0.45 or 0.2 milliseconds in length. The frequency of the stimulation was increased in steps from 5 to 800 and from 10 to 2500 signals per second respectively at each length. The irritability curve after a single stimulus was determined by two identical rectangular maximal impulses with a duration of 0.2 milliseconds.

The distance between impulses was gradually increased from 0.1 to 100 milliseconds. This increase was carried out gradually (Fig. 1): in the first range were 11 tests of the contractions. In the first test the time between impulses was less than 0.1 millisecond, in the second it was 0.2, then 0.3, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.7 milliseconds. In the second range the first test was at an interval of less than 1.3 milliseconds, then 1.5, 2.2, 3.0, 4.0 etc. (the last, fourteenth, test was at an interval of 22 milliseconds). In the third range, consisting of 13 tests, the interval grew in the following order: less than 5, 7, 12, 17, 22, 30, 40, 50, 60, 70, 85, 97 and more than 105 milliseconds. As the interval increased the following phases appeared: 1) absence of summation (absolute refractory phase), 2) increasing summation, 3) maximum summation and 4) decreasing summation.

EXPERIMENTAL RESULTS

The strength-duration curve was determined in 22 experiments. In all cases decreased muscular irritability to indirect stimulation began after the disappearance of the pupillary reflex. In 15 cases the rise in the thresholds reached 20 and even 50%. The thresholds for short impulses increased more, proportionately, than the ones for prolonged ones. The size of the contraction during stimulation by single impulses decreased 2-4 times (Fig. 2).

Fig. 2. Action of ether narcosis on contractibility. a) Muscular contraction 7 minutes after disappearance of the reflex; b) the same after 13 minutes; c) after 28 minutes. Stimulation by means of single rectangular impulses with a length of 140 milliseconds with increasing amplitude. The numerals indicate the amplitude of the stimulating impulses.

The dynamics of irritability after a single stimulation (ability to summate 2 impulses) was determined in 24 experiments, 9 of which were controls. Normally, summation begins at an interval of 0.9-1 millisecond, reaches a maximum at an interval of 3-4 milliseconds and begins to decrease when the interval is increased to 15-20 milliseconds. During narcosis, after the disappearance of the pupillary reflex, in 2/3 of the cases an earlier completion of the phase of maximal summation by 5-10 milliseconds was observed (shortening 1.5-2 times, see Fig. 1). Other changes were not observed.

The lability was determined in 20 experiments, 8 of these controls. In the majority of cases the response to stimulation decreased evenly along the entire scale of frequencies, without losing its tetanic nature. In 5 experiments the contractibility in response to stimulation with a frequency of 5-10 signals per second fell relatively more rapidly than at medium and optimal frequencies.

All the described changes in the parameters of the neuro-muscular apparatus appeared, as a rule, 15-30 minutes after the disappearance of the pupillary reflex, i.e. under deep narcosis. The re-establishment of the original values sometimes began immediately after the cessation of the narcosis and the appearance of the reflexes, but more often it was delayed by tens of minutes. Severance of the nerve did not eliminate the effect of the narcosis on the neuro-muscular apparatus.

The fact that ether diminishes and stops the contraction of the muscle during indirect stimulation enabled some authors [10] to establish the curarimimetic action of this anesthetic. We traced the action of a new synthetic curarimimetic preparation – diplatsin – on the neuro-muscular apparatus of the warm-blooded animal.

When stimuli were applied at short intervals (0.3-0.4 seconds) during the investigation of refractoriness, the first effect, and sometimes the second also, exceeded the subsequent considerably (phenomenon of diminution). Consequently, the picture of changes in irritability was distorted after a single stimulus (if the test stimuli were administered rapidly enough one after the other), since the impression was created of a rise and rapid fall of irritability after each prolonged pause regardless of the length of the intervals between the impulses. When the interval between tests was increased to approximately 2 seconds, the phenomenon of diminution disappeared.

Investigation with a sufficient pause between tests permitted the establishment of the fact that the dynamics of irritability after a single impulse did not undergo any substantial changes. The lability of the neuro-muscular apparatus fell sharply.

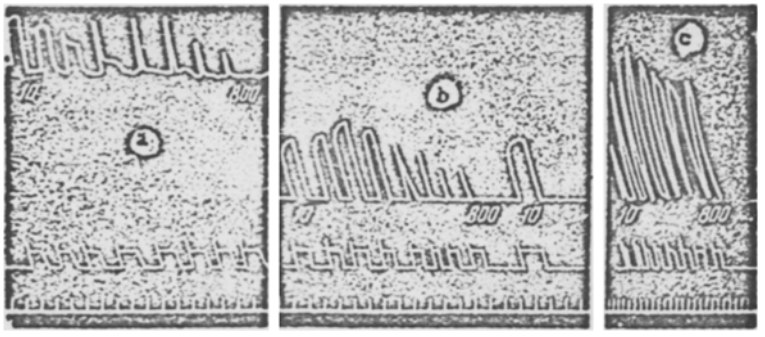

Fig. 3. Changes in lability during administration of diplatsin.
a) 2 minutes after administration of the preparation; b) after 8 minutes;
c) after 15 minutes – complete re-establishment of lability.
Curves (top to bottom): record of muscular contractions, stimulus marker, time marker (5 seconds). Stimulation by impulses of 0.45 milliseconds.
Numbers indicate the frequency of the stimulation in cps.

Frequencies above 50 and even 30 signals per second caused a sharply evidenced pessimal reaction in the form of considerable initial spasms (Fig. 3).

We observed the leveling and paradoxical phases of the reaction of the curarized neuro-muscular apparatus, as described by N. E. Vvedensky. The indicated changes in lability were fully evident during direct stimulation of the muscle also, when the platinum electrodes were inserted subcutaneously at the cranial and caudal end of the cuffed muscle.

Our data on the changes in the lability of the neuro-muscular apparatus in response to the administration of diplatsin coincide basically with the results of other authors [2, 12] who used tubocurarine. We did not find a predominant depression of the response to infrequent rhythms and a shortening of the refractory phases during curarization, as observed by N. A. Yudenich [8] and N. M. Bunina [1], who worked with neuromuscular frog preparations.

The difference between a single wave of stimulation and a wave of stimulation in a rhythmic row was clearly evident during curarization.

The capacity to summate and refractoriness, determined by means of 2 impulses, did not suffer substantial changes. However, when a row of such impulses follows (with a sufficiently high frequency), the activity of the muscle is disrupted, the contraction disappears. Consequently, during curarization profound disturbances of the summating capacity (in particular, change in the refractory phase as well) began in the very course of the stimulation of the neuro-muscular apparatus. The test with 2 impulses, on the other hand, reflects more or less adequately only the least changed stage of this process. This is confirmed by the considerable size of the initial spasms with the subsequent decrease of the contraction to zero. Changes in the refractory phase during the very course of the process of irritation were described in the literature, for example by L. G. Trofimov, [6] during pessimal stimulation of the neuro-muscular apparatus.

The phenomenon of diminution indicates that during curarization there is a prolonged subsequent depression of the contractility of the neuro-muscular apparatus after each contraction.

We can state that this narcotic has a depressant action with respect to the action of ether on the neuro-muscular apparatus.

The capacity to summate frequent impulses is not affected in the case of 2-3 impulses, nor in the case of numerous ones (at the ether concentrations used in our experiments). It can be supposed that the summation of infrequent stimuli is hampered. The shortening of the phase of maximal summation points to this, as well as experiments in which the muscular effect during rhythmic low-frequency stimulation decreases to a greater extent than during stimulation at higher frequencies. The phenomenon of diminution was absent during the action of ether.

Tests in which the nerve was severed proved the depressant effect of ether on the peripheral link of the neuro-muscular apparatus. If it is taken into consideration that changes in the electrical activity of the nerve and of the contractility of the muscle (during direct stimulation) begin at considerably greater concentrations of ether than of narcotics [17, 16], the most likely point of application of ether is the region of the neuro-muscular junction. In addition, as N. E. Vvedensky [3] observed earlier, the peripheral portions of the nervous system – in this case the motor neurons – are considerably less sensitive to narcosis than are the cells and synapses of the cortex.

The effect of ether on the neuro-muscular apparatus is especially clear with the combination of narcotic and curarimimetic, since then synergism of the action of both substances is observed. How far this synergism extends is shown by the following fact. During ether narcosis of a rabbit 5 days after repeated administration of diplatsin (1-1.2 mg/kg) we observed profound disturbance of the functioning of the neuro-muscular apparatus of rapid onset, in particular, obvious changes in lability typical of affection by curare. Repetition of the narcotization of the same animal 5 days later did not give such an effect. As is known, curarimimetics are quickly destroyed in the system and have a highly transitory action [5, 13]. However, their after-effect can be evident even after a considerable time during supplementary affection of the neuro-muscular apparatus.

Thus, ether narcosis, as also curarimimetic administration, has a depressant action on the peripheral section of the neuro-muscular apparatus of the warm-blooded animal. However, the mechanism of the action of both substances differs in many respects. During approximately the same stage of disrupted contractility, under ether narcosis the ability to summate infrequent impulses disappears, the summation of frequent impulses during double and rhythmic stimulation is retained. During the administration of diplatsin, the summation of two impulses is not disturbed, although during rhythmic stimulation the capacity to summate is retained for infrequent impulses only (to 50 per second), the summation of more frequent impulses is disturbed (sharp fall of lability), the recovery period after a single contraction is substantially increased (phenomenon of diminution).

LITERATURE CITED

[1] N. M. Bursina, Abstracts of Reports of the VIII Scientific Session of the Smolensk Medical Institute,* (Smolensk, 1954), pp. 37-39.

* In Russian.

[2] A. V. Valdman and V. V. Zakusov, Farmakol. i Toksikol. 15, 3, 4-9 (1952).

[3] N. E. Vvedensky, Complete Collected Works,* Vol. 4, p. 122 (1953).

[4] A. V. Dokukin, Byull. Eksptl. Biol. i Med. 36, 4, 10, 71-73 (1953).

[5] M. D. Mashkovsky and A. I. Briskin, Farmakol. i Toksikol. 5, 24-32 (1952).

[6] L. G. Trofimov, Fiziol. Zhur. SSSR 35, 2, 182-189 (1949).

[7] I. M. Tykvich and B. S. Rabinovich, Mechanisms of Pathological Reactions,* (Leningrad, 1949), No. 11-15, pp. 77-80.

[8] N. A. Yudenich, Byull. Eksptl. Biol. i Med. 20, 9, 41-42 (1945).

[9] E. G. Gross and S. C. Cullen, J. Pharmacol. 78, 2, 356-365 (1943).

[10] K. Naess, Acta Pharmacol. Toxicol. Scand. 6, 1, 81-91 (1950).

[11] K. Naess, Acta Physiol. Scand. 19, 350-369.

[12] K. Naess, Acta Pharmacol. Toxicol. Scand. 8, 2, 137-148 (1952).

[13] W. C. North and R. K. Richards, Exptl. Med. Surg. 8, 2/4, 336-345 (1950).

[14] T. Poulsen and O. Secher, Acta Pharmacol. Toxicol. Scand. 5, 3, 196-212 (1949).

[15] T. Poulsen and O. Secher, Acta Pharmacol. Toxicol. Scand. 5, 3, 213-221 (1949).

[16] W. Sefton, A. Forbes and K. Mc Intosh, Am. J. Physiol. 40, 503-513 (1916).

[17] O. Secher, Acta Pharmacol. Toxicol. Scand. 6, 4, 371-385 (1950).

[18] O. Secher, Acta Pharmacol. Toxicol. Scand. 7, 1, 83-93 (1951).

* In Russian.