THE EFFECT OF NARCOTICS ON SKELETAL MUSCLE REACTIVITY TO ACETYLCHOLINE AND POTASSIUM IONS

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In this work, we report experimental data indicating that narcotics can either diminish or completely prevent potassium contracture of a skeletal muscle, but do not affect acetylcholine contracture.

EXPERIMENTAL METHODS

A grass frog's isolated rectus abdominis muscle was placed in a small jar containing a Ringer's solution, under conditions of continuous aeration. One hour after isolation of the muscle, supraliminal concentrations of potassium chloride (1 : 1000-1 : 1300, most often 1 : 1500) were added to the solution washing the muscle. The muscle's contractions were recorded on the smoked tape of a kymograph cylinder for two minutes. At the end of this time, the Ringer's solution was changed several times, and then the positive reaction of the muscle to acetylcholine (1 : 5 million - 1 : 1 million) was tested in 5 out of 39 experiments. After a fresh washing out, one of the following narcotics was added to the jar: ether (0.1-0.2 ml per 10 ml Ringer's solution), isoamyl alcohol (1 : 1000), amytal sodium (1 : 10000), pentothal (1 : 4-2000) and Neuronal (1 : 4000). The reactivity of the muscle to potassium ions and acetylcholine in the above concentration was then tested again after 15-60 min, in all 39 experiments this time. Only one of the narcotics, used once, was tested in each experiment.

The same experiments were then performed on a rat's diaphragm. The preparation was prepared according to Bülbring [3] and transferred to a small bath containing Tyrode's solution (100 ml) saturated with oxygen through a hollow glass hook. A general-purpose thermostat was used to keep the temperature of the nutrient solution at 24-25°. The nerve was put on electrodes of Bülbring's design. Stimulation was done by means of an electron stimulator generating square-wave impulses 0.5 msec in duration and 12 imp/min in frequency. The contractions were recorded on the smoked tape of a kymograph cylinder.

The order of the experiments was as follows: the contractile reaction of the diaphragm was tested under conditions of indirect stimulation of the latter; the stimulator was then turned off, and the reactivity of the muscle to potassium ions was tested by adding a potassium chloride solution in supraliminal concentrations (1 : 300-1 : 250) to the bath containing the muscle. The diaphragm contracture was recorded for three minutes, after which the potas-

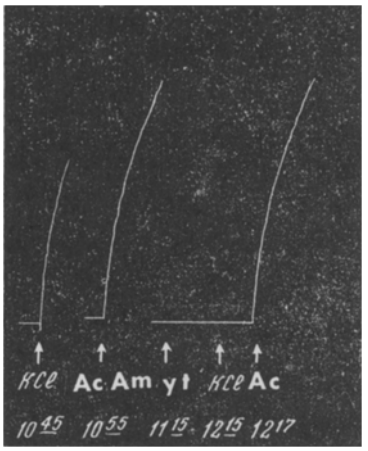

Fig. 1. Effect of amytal sodium on potassium (prevented development) and acetylcholine (did not prevent development) contractures of a frog's rectus abdominis muscle. Concentrations: potassium chloride 1 : 1000; acetylcholine 1 : 1000000; amytal sodium 1 : 1000000 for 60 min, then potassium chloride 1 : 1000, acetylcholine 1 : 1000000.

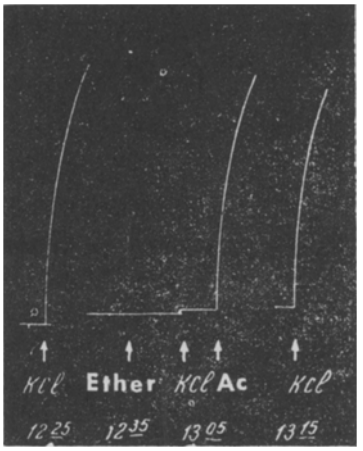

Fig. 2. Effect of ethyl ether on potassium (prevented development) and acetylcholine (did not prevent development) contractures of a frog's rectus abdominis muscle. Concentrations: potassium chloride 1:1000, washed out; ethyl ether 0.2 ml per 10 ml for 30 min; potassium chloride 1:1200; acetylcholine 1:1000000, washed out; potassium chloride 1:1000.

sium chloride was washed out by changing the Ringer's solution three times. Electric stimulation of the nerve was resumed 5-10 min later, with the stimulator operating under the same conditions as before. A narcotic was added to the bath (1 : 750-500 hexenal, 1 : 3000-1000 amytal sodium, 1 : 2000-1000 Neuronal) on a background of continuous rhythmic contractions of the muscle. The stimulation was stopped after 35-80 min, and the muscle's reaction to potassium chloride tested again, the latter being used in the same concentrations as in the control test.

EXPERIMENTAL RESULTS

All the experimental narcotics considerably reduced or even totally inhibited potassium contracture of a frog's rectus abdominis muscle, but did not inhibit the acetylcholine reaction (Figs. 1 and 2, Table 1).

The height of the acetylcholine contractures in the control and experimental tests showed that the narcotics did not reduce the amplitude of the acetylcholine contraction of the muscle in any of the five experiments. In a

TABLE 1. Effect of Narcotics on Reactivity of Frog's Rectus Abdominis Muscle to Potassium Ions (1 : 1000-1 : 2000) and to Acetylcholine (1 : 5 million-1 : 1 million)

Total number of experiments	Name and concentration of narcotic	Potassium contracture			Reaction to acetylcholine
		inhibited	diminished	unchanged	
10	Ethyl ether 1 : 100-1 : 200 (0.1-0.2 ml per 10 ml)	6	2	2	Retained
8	Isoamyl alcohol 1 : 1000	3	4	1	"
10	Amytal sodium, 1 : 10000	9	1	0	"
5	Pentothal, 1 : 4000-1 : 2000	2	3	0	"
6	Neuronal, 1 : 4000	5	1	0	"
Total . . . 39		25	11	3	

number of tests, the narcotics even induced some increase in the height of the acetylcholine contracture. The increase in the amplitude of the contraction cannot be ascribed to the inhibitory effect of the narcotics on cholinesterase, as certain authors have assumed on the basis of both in vitro and in vivo experiments. Specific investigations have been conducted which exclude this possibility: on a tonic muscle exhibiting no acetylcholine pessimum (frog's rectus abdominis muscle), narcotics inhibit cholinergic guanidine tremors, preventing contracture; if narcotics inhibited hyperkinesia by inhibiting cholinesterase and thereby promoting an accumulation of a surplus of acetylcholine, contracture would rapidly develop when the hyperkinesia of a tonic muscle is inhibited [1].

The experiments performed on a rat's diaphragm showed that, in the experimental concentrations, the narcotics either did not change the muscle's reaction to indirect stimulation at all or only slightly reduced it (decrease in the amplitude of the contractions did not exceed 15-20% of the original). There was a considerable decrease, however, in the height of the potassium contracture: hexenal and amytal sodium reduced in 70% on the average,

Neuronal, by as much as 80%. Neuronal not only induced particularly strong inhibition of the potassium reaction of the muscle, but also diminished its reaction to indirect stimulation more than the other narcotics.

If the action of the narcotic was sufficiently prolonged (over 2 hrs), total inhibition of the muscle's reaction to potassium ions occurred, although the indirect excitability was retained (Fig. 3, a, b, Table 2). The effect of the narcotics was reversible: after the muscle had been rinsed 3-15 min with Tyrode's solution, the height of the potassium contracture equalled the original.

The following main differences in the reactions of the muscles of cold- and warm-blooded animals were observed: 1) the potassium chloride concentrations inducing definite contracture of the diaphragm were 6-7 times higher than those exerting an analogous effect on the frog's rectus abdominis muscle; 2) the concentrations of the narcotics which reduced or inhibited potassium contracture of the diaphragm were 4-5 times as high as those required for a similar effect on the frog's rectus abdominis muscle.

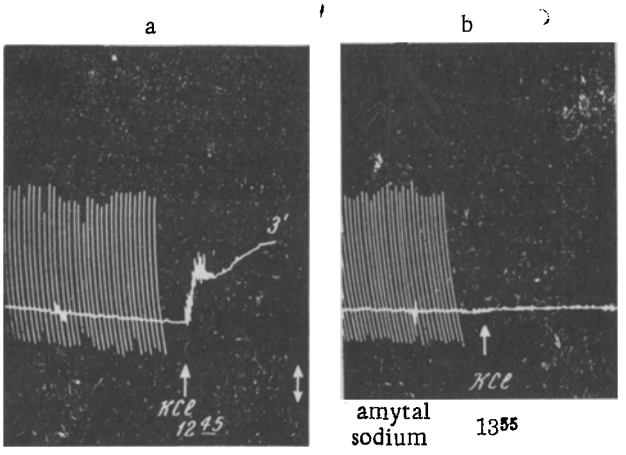

Fig. 3. Effect of amytal sodium on potassium contracture and indirect excitability of a rat's isolated diaphragm. A) Muscle tremors induced by indirect stimulation, potassium chloride added (1 : 250) when stimulation ceased, tremors and contracture effected by KCl; B) muscle contractions during 45 min influence of amytal sodium (1 : 1000) in response to indirect stimulation; potassium chloride (1 : : 250) added when stimulation ceased. The tiny fluctuations recorded on the kymogram while the muscle was at rest are the movements of the rod caused by the aeration of the Tyrode's solution.

TABLE 2. Effect of Narcotics on Reactivity of a Rat's Isolated Diaphragm to Potassium Ions (1 :300 - 1 : 200) and Indirect Stimulation

Total Number of experiments	Name and concentration of narcotic	Potassium contracture			Number of experiments with indirect excitability	Indirect excitability	
		inhibited	reduced 1/3-1/5	unchanged		unchanged	slightly reduced
8	Amytal sodium, 1 : 3000-1 : 1000	2	6	0	3	2	1
6	Hexenal, 1 : 750-1 : 500	1	5	0	6	4	2
9	Neuronal, 1 : 2000-1 : 1000	4	5	0	5	2	3
Total . . . 23		7	16	0	14	8	6

Since the rat's diaphragm did not react in our experiments to acetylcholine introduced from without, we studied the cholinergic reaction of the muscle under conditions of its indirect stimulation. There are essential differences in the excitation processes caused by exogenous and endogenous acetylcholine; the results obtained in the experiments testing the reaction of the frog s muscle to acetylcholine and that of the rat's diaphragm to indirect stimulation when the muscles were poisoned with narcotics can therefore be compared only conditionally. The experimental data in-

dicate, however, that in both cases, the muscle's contractile reaction to potassium ions was inhibited by narcotics considerably more than the reaction to acetylcholine was. These data suggest that the skeletal muscles contain a structural component which selectively reacts to potassium ions more than to acetylcholine and is inhibited by narcotics. The exact nature of this component is discussed in V. M. Karasik's article [2].

SUMMARY

Narcotics reduce or even depress potassium contracture of the frog rectus abdominis, not only without decreasing, but often even with increasing its acetylcholine contracture. Analogous data were obtained on the rat phrenicus-diaphragm preparations. A suggestion was made on the presence of structural component in the skeletal muscle reacting more selectively on the potassium ions than on the acetylcholine; this component is depressed by narcotics. Augmentation of the acetylcholine contracture under the effect of narcotics does not depend on the cholinesterase depression, since this possibility is exluded by investigations of V. M. Karasik and E. V. Moreva in 1958.

LITERATURE CITED

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3. E. Bülbring, Brit. J. Pharmacol. Vol. 1 (1946), p. 38.

All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
