ROLE OF SODIUM IONS IN REGULATION OF MYOCARDIAL CONTRACTIONS

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Facilitation of contractions of the frog myocardium were investigated in solutions with a reduced sodium ion concentration in response to stimulation at different frequencies. The degree of facilitation was reduced in a solution with low sodium concentration and the maximum of facilitation was displaced into the region of low frequencies. The time constant of facilitation depended on the sodium ion concentration in the external solution. In a series of ten contractions in solution of low sodium concentration the amplitude of the contractions was not stabilized.

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Existing data [5, 8, 10] suggests that the strength of myocardial contractions is mainly determined by the competitive ratio between sodium and calcium ion concentrations inside the cells. A change in the sodium concentration has a direct effect on fixation of calcium ions by the elementary contractile structures of the isolated sarcotubular elements of the rabbit myocardium. Lowering the sodium concentration in the medium led to an increase in calcium fixation and vice versa [9]. The connection between action potential parameters and the characteristics of contractions of the myocardial cells [4], and also the dependence of duration of the action potentials and their aftereffects on the rate of work of the electrogenic sodium pump [1, 2] suggest that sodium ions also play a role in the regulation of parameters of the contractile mechanism.

To investigate this problem the contractile responses of the myocardium of cold-blooded animals were studied in response to paired stimuli applied at different intervals, and to repetitive stimulation, varying the sodium ion concentration in the medium.

EXPERIMENTAL METHOD

The isolated perfused ventricle of the frog Rana temporaria was placed in a small bath with saline [3] containing 110 mmole NaCl. The deficiency of sodium ions in the solutions of low sodium concentration was made good by an equivalent quantity of lithium ions. For the first 10 min the preparation, kept in normal solution, was stimulated at 0.1 Hz, then followed a pause of 3 min, after which one or two stimulating pulses were applied in order to record the initial amplitude and duration of the contractions. Contractions in response to pairs of stimuli were next investigated: the intervals between the two stimuli of each pair varied from 30 to 1-0.8 sec and the pause between each pair lasted for 40-60 sec. The duration of the pauses was chosen separately for each preparation. After paired stimulation, series of ten contractions in response to stimulation at different frequencies (from 0.2 to 1 Hz) were investigated. The rest period after each series was 60-90 sec. The course of the experiment in the test solutions was the same.

The main index for the changes in myocardial contractile activity was "facilitation" of the contractions: the increase in amplitude of the contractions during a change in the distances between the first (background) and second (test) contraction. In a series of ten contractions the facilitation of each contraction was determined relative to the first. The numerical values of the facilitation was determined by the formula:

$$P = \frac{A_n}{A_1} - 1,$$

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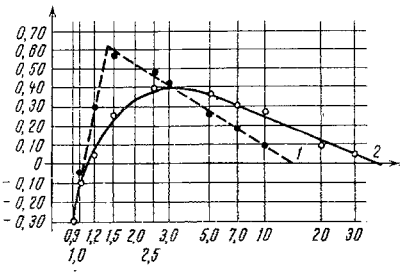

Fig. 1

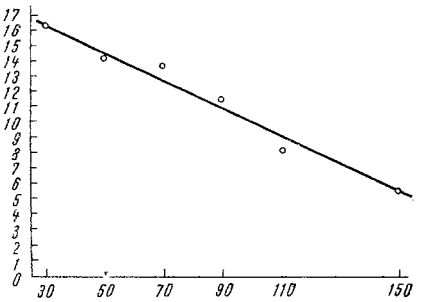

Fig. 2

Fig. 1. Dependence of facilitation on intervals between stimuli and on concentration of extracellular sodium. 1) Normal solution; 2) solution of low sodium concentration (30 mM NaCl). Ordinate: degree of facilitation (in relative units); abscissa: interval between stimuli (in sec; logarithmic scale).

Fig. 2. Time constant (τ) of facilitation as a function of sodium ion concentration in external solution. Ordinate: τ (in sec); abscissa: sodium ion concentration (in mM).

where P is the degree of facilitation; A_n the amplitude of the test contraction; A_1 the amplitude of the background (first) contraction.

EXPERIMENTAL RESULTS

The course of facilitation during paired stimulation in a solution with a normal content of sodium ions (110 mmole) is shown in Fig. 1 (broken line). Facilitation appeared when the interval between stimuli was 15 sec or less. Facilitation reached its maximum (0.6±0.08) when the interval was 1.35±0.03 sec. A further decrease in the interval between stimuli reduced the degree of facilitation or reversed its value to negative (this phenomenon occurred during a marked diastolic contraction, for the amplitude of the test contraction in all calculations was taken to be the total amplitude minus the diastolic contraction). The continuous line in Fig. 1 shows facilitation in a solution with lowered sodium ion concentration (30 mmole NaCl + 80 mmole LiCl). Under these conditions facilitation appeared when the interval between stimuli was 30 sec. The greatest degree of facilitation (0.4±0.05) was recorded when the interval between stimuli was 3.2±0.2 sec. With a decrease in the interval between stimuli, the degree of facilitation was reduced. In solutions of low sodium concentration, the maximum of facilitation was thus shifted into the region of long intervals between stimuli, and its degree was reduced. The change in the time constant of facilitation in solutions with different concentrations of sodium ions is shown in Fig. 2. A concentration of 30 mmole NaCl corresponds to the highest time constant (16.4 sec). With an increase in sodium concentration the time constant was reduced, reaching 5.5 sec when the NaCl concentration was 150 mmole. The relationship between time constant of facilitation and sodium concentration in the external solution was linear in character. In series of 10 contractions in normal solution the greatest increase in amplitude occurred when the frequency of stimulation was 0.8 Hz (Fig. 3), and in solution with low sodium concentration at a frequency of 0.5-0.6 Hz. Stabilization of the amplitude in normal solutions during stimulation of low frequencies (0.2-0.4 Hz) occurred by the 5th-6th contraction, and at high frequencies (0.8-1 Hz) by the 8th-9th contraction. No stabilization of amplitude took place in solutions of low sodium concentration. The amplitude of the contractions in solution with low sodium concentration, under the same conditions of stimulation, was much higher than in normal solution. The time constants of increase in amplitude of the contractions in normal and low-sodium solutions were not significantly different.

The results of these experiments show that reducing the sodium concentration in the medium affects not only the absolute increase in amplitude of the background and test contractions, but also subsequent facilitation. In a medium with low sodium concentration facilitation occurs in a considerably wider zone between background and test contractions than in a normal medium.

On the assumption that the contractile activity of the myocardial cells is regulated by interaction between ions [6, 7], and that sodium ions control myocardial contractility by their action on the fixation of

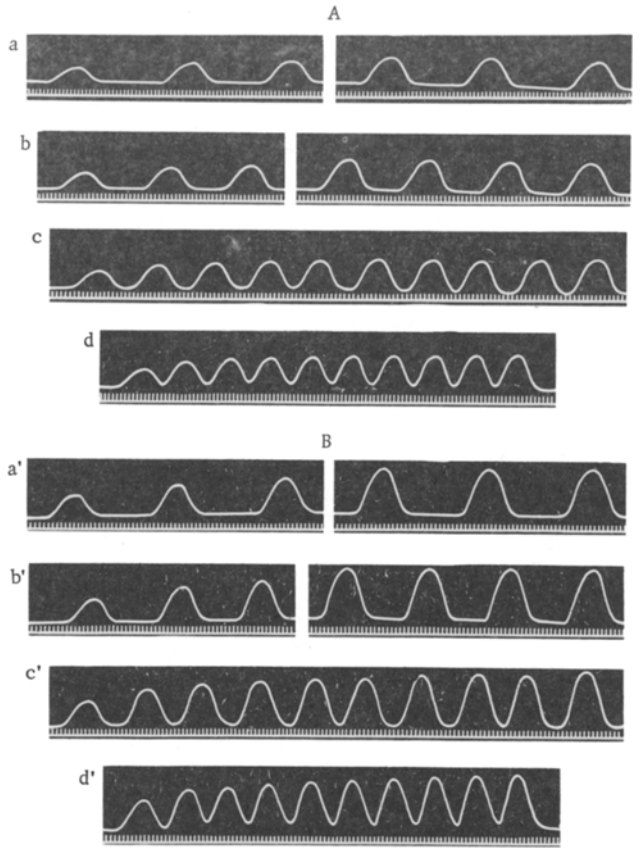

Fig. 3. Series of ten contractions in normal (A) and low-sodium (B) solutions for different frequencies of stimulation: 0.3 (a, a'), 0.45 (b, b'), 0.8 (c, c'), and 0.9 Hz (d, d').

calcium ions, the results obtained can be explained as follows. The increase in amplitude of the contractions in a rhythmic series (positive staircase) depends on at least two interconnected processes: movement of sodium ions from intracellular areas where they complete with calcium ions, and accumulation of calcium ions. The increase in calcium concentration in the system of contractile filaments and the outflow of calcium are determined by the rate of active pumping of sodium from the cell. Under ordinary conditions these processes take place at a sufficiently high velocity and the reverse transport of sodium compensates for the outflow of calcium from the contractile elements. In a medium with low sodium concentration ionic interaction is disturbed: the number of sodium ions entering the cell in the course of each cycle of excitation is reduced, and a correspondingly larger number of anionic loci in the cell is occupied by calcium ions, and this is expressed by an absolute increase in amplitude of the contractions. Meanwhile, a decrease in the intracellular sodium concentration reduces the efficiency of work of the sodium pump, slowing the outflow of sodium from the cell and leading to retention of calcium in the system of contractile proteins. The uncompensated outflow of sodium from the cell and retention of calcium ions in each contractile cycle must naturally lead to prolongation of the facilitation time and to lack of stabilization of the amplitude of contractions in a rhythmic series.

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