ACTION OF Na^+, K^+, and Ca^{++} IONS ON THE DURATION OF THE PREAUTOMATIC PAUSE OF THE HEART

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The duration of the preautomatic pause arising after rapid electrical stimulation of the Purkinje fibers of the dog's heart, fibers of the frog's sinus venosus, and the ventricles of the isolated rabbit's heart, was investigated. Action potentials of the cardiac pacemakers were recorded with microelectrodes. In response to brief stimulation (10-20 sec) and a lowered K_{int}/K_{ext}, Na_{ext}/Na_{int}, or Ca_{ext}/Ca_{int} ratio, the automatic activity was depressed more strongly, with a consequent lengthening of the preautomatic pause after the end of electrical stimulation. Conversely, in response to prolonged electrical stimulation (3 min) and a lowered K_{int}/K_{ext}, Na_{ext}/Na_{int}, or Ca_{ext}/Ca_{int} ratio, the depression of automatic activity was reduced and the preautomatic pause after the end of stimulation was shortened. These results explain the conflicting data in the literature on the action of these ions on the duration of the preautomatic pause of the heart.

KEY WORDS: myocardium; automatic rhythmic activity; sodium, potassium, and calcium ions.

High-frequency electrical stimulation can temporarily depress the cardiac pacemaker activity [2, 3, 5, 7, 9]. The depression of automatic activity is reflected in the appearance of a preautomatic pause after the end of electrical stimulation.

Data in the literature on the action of Na^+ and K^+ ions on the duration of the preautomatic pause are contradictory. According to some findings, a decrease in the extracellular concentration of Na^+ ions causes shortening of the preautomatic pause [4, 6], whereas an increase in the extracellular concentration of K^+ ions leads to a decrease in the depression of automatic activity during fast electrical stimulation of the cardiac pacemakers [4, 7, 8]. According to other observations, in response to fast electrical stimulation of the Purkinje fibers of the ventricle of the dog's heart, an increase in the extracellular K^+ or a decrease in the extracellular Na^+ concentration depresses automatic activity and lengthens the preautomatic pause after the end of stimulation [5].

It was decided to study the action of different concentrations of Na^+, K^+, and Ca^{++} ions on the duration of the preautomatic pause arising in response to previous electrical stimulation of varied duration.

EXPERIMENTAL METHOD

The test objects were Purkinje fibers of the dog's heart (10 animals), the isolated sinus venosus of frogs (20), and the isolated hearts of rabbits (20) with complete atrioventricular block. Each object served for 2-3 experiments. The total number of observations during the various experiments was 120.

Preparations of the Purkinje fibers isolated from the dogs' cardiac ventricles and the isolated rabbits' hearts were perfused with Tyrode solution of the following composition (in mM): NaCl 130, KCl 2.6, $CaCl_2$ 1.8, $MgCl_2$ 1, $NaHCO_3$ 12, Na_2HPO_4 0.4, glucose 5.5; pH 7.3. The solution was saturated with 95%

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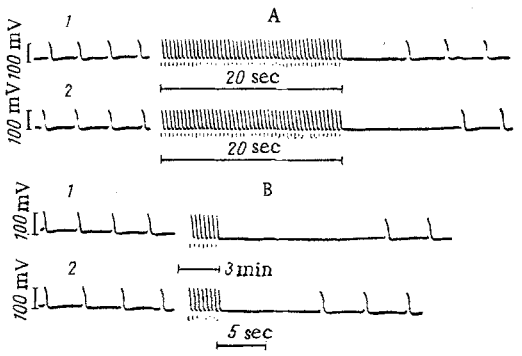

Fig. 1

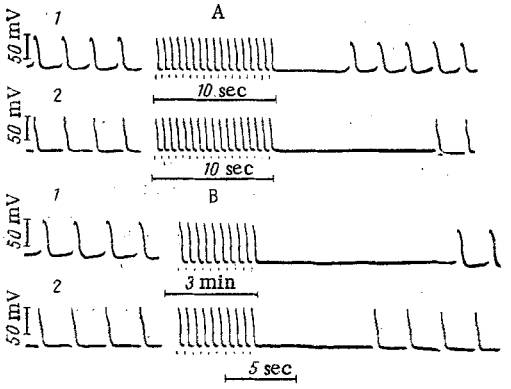

Fig. 2

Fig. 1. Action of a double concentration of K^+ ions on the duration of the preautomatic pause arising after brief (A) and long (B) electrical stimulation: 1) control preautomatic pause during perfusion with ordinary Tyrode solution; 2) preautomatic pause in an increased concentration of K^+ ions. Record of action potentials of a single Purkinje fiber of a dog's heart. Frequency of electrical stimuli 140/min. Times of electrical stimulation marked by dots.

Fig. 2. Action of half-concentration of Na^+ ions on duration of preautomatic pause arising after brief (A) and long (B) electrical stimulation: 1) control preautomatic pause during perfusion with ordinary Ringer's solution; 2) preautomatic pause in a reduced concentration of Na^+ ions. Record of potentials of a single fiber of the frog sinus venosus. Frequency of electric stimuli 100/min.

O_2 and 5% CO_2. The temperature of the solution was 36°C, and the rate of perfusion 10 ml/min. The isolated frogs' sinus venosus was perfused with Ringer's solution of the following composition (in mM): NaCl 110, KCl 2.5, $CaCl_2$ 1.8, $NaHCO_3$ 2.4; pH 7.3.

The duration of the preautomatic pause was studied: 1) with KCl or $CaCl_2$ excluded from the perfusion fluid or with a two- to threefold increase in the concentration of one of these salts; 2) with a two- or fourfold decrease in the NaCl concentration (equimolar amounts of sucrose were added to maintain the isotonicity of the solution) or with an increase of 1.5 times in the NaCl concentration.

Potentials were recorded intracellularly with glass microelectrodes from single spontaneously contracting Purkinje fibers of the heart of the warm-blooded animals or from the pacemaker fibers of the sinus venosus of the frog. In the experiments on the isolated rabbits' hearts the ventricular ECG was recorded.

Automatic activity of the cardiac pacemakers was depressed by high-frequency electrical stimulation. Stimuli with a duration of 2-5 msec and a voltage just above the threshold were applied. The frequency of the stimuli was 2-3 times higher than that of spontaneous excitation. A brief but distinct preautomatic pause and a pause twice to three times longer were induced in each experiment. This was done by increasing the duration of electrical stimulation from 10-20 sec to 3 min (keeping the frequency of the electrical stimuli constant). With these different periods of stimulation it was possible to examine the effect of the various ions on the duration of the preautomatic pause most clearly and reliably.

EXPERIMENTAL RESULTS

In all the experiments, whether on the Purkinje fibers of the dog's heart, on the fibers of the frog sinus venosus, or on the ventricles of the isolated rabbit's heart, the same general rule was clearly observed: During brief electrical stimulation (10-20 sec) an increase in the extracellular concentration of K^+ ions or a decrease in the extracellular concentration of Na^+ ions lengthened the preautomatic pause (by 2-3 times). An increase in the extracellular concentration of Ca^{++} ions, on the other hand, shortened the pause (by half).

During long electrical stimulation (3 min) these same ions had quite the opposite action: An increase in the extracellular concentration of K^+ ions or a decrease in the extracellular concentration of

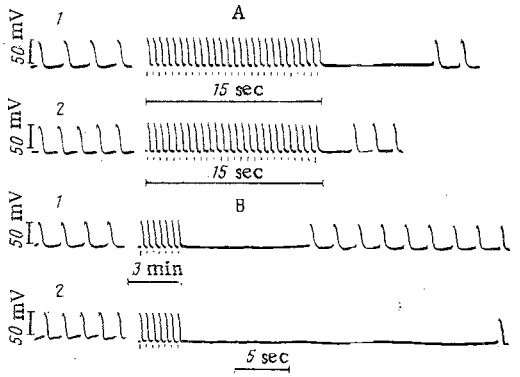

Fig. 3. Action of a double concentration of Ca^{++} ions on duration of preautomatic pause arising after brief (A) and long (B) electrical stimulation: 1) control preautomatic pause during perfusion with ordinary Ringer's solution; 2) preautomatic pause in an increased concentration of Ca^{++} ions. Record of action potentials of a single fiber of the frog sinus venosus. Frequency of electrical stimuli 100/min.

Na^+ ions shortened the preautomatic pause (by 2-3 times) whereas an increase in the extracellular concentration of Ca^{++} ions lengthened it significantly.

The changes in duration of the preautomatic pause after an increase in the extracellular concentration of K^+ ions in response to brief and long stimulation are illustrated in Fig. 1. During perfusion of the Purkinje fibers of the isolated atrioventricular bundle of the dog's ventricle with ordinary Tyrode solution the duration of the control preautomatic pause after 20 sec of electrical stimulation was 10 ± 1.3 sec. During perfusion with a solution containing twice the KCl concentration the preautomatic pause after 20 sec of electrical stimulation was lengthened to 19 ± 2.1 sec.

In experiments on these same preparations after the end of a long period (3 min) of electrical stimulation and during perfusion with ordinary Tyrode solution the duration of the control preautomatic pause was 24 ± 3.1 sec. After 3 min of electrical stimulation and during perfusion with a solution containing double the concentration of KCl the preautomatic pause was shortened to 13 ± 1.2 sec.

The changes in the duration of the preautomatic pause with a decrease in the extracellular concentration of Na^+ ions and in response to brief and long electrical stimulation are shown in Fig. 2. During perfusion of the isolated sinus venosus of the frogs with ordinary Ringer's solution the duration of the control preautomatic pause after 10-20 sec of electrical stimulation was 7 ± 1.1 sec. With a decrease in the concentration of Na^+ ions by half the preautomatic pause was increased to 16 ± 2.1 sec.

In the experiments on these same preparations and during perfusion with ordinary Ringer's solution, the duration of the preautomatic pause after 3 min of electrical stimulation was 12 ± 1.3 sec. After the end of electrical stimulation and in half the concentration of Na^+ ions, the duration of the preautomatic pause was reduced to 6 ± 1.0 sec.

The effect of an increased concentration of Ca^{++} ions together with brief and long electrical stimulation is illustrated in Fig. 3. In experiments on the same preparations of the isolated sinus venosus of frogs, doubling the concentration of Ca^{++} ions led to shortening of the preautomatic pause (from 8 ± 1.3 to 2 ± 0.5 sec) after brief electrical stimulation (10-20 sec), but to lengthening of the pause compared with the control (from 13 ± 1.4 to 28 ± 2.5 sec) after long electrical stimulation (3 min).

Similar results were obtained during the investigation of the action of K^+, Na^+, and Ca^{++} ions on the duration of the preautomatic pause arising after the end of fast electrical stimulation of the ventricles of the isolated rabbit's heart with a complete atrioventricular block.

Depression of the automatic activity of the cardiac pacemakers during high-frequency electrical stimulation arises as the result of imbalance between passive and active ion transport [1]. The general rule for the action of Na^+, K^+, and Ca^{++} ions on the duration of the preautomatic pause stated above may therefore rest, perhaps, on the following explanation. During brief electrical stimulation, when the disturbances of the ionic gradients inside and outside the cell are still small, a change in the concentration of Na^+, K^+, or Ca^{++} ions affects predominantly the passive ion transport. During long electrical stimulation, when there is a considerable shift of ionic gradients inside and outside the cell, the effect of these ions on active ion transport begins to predominate.

The results of these experiments explained the, at first glance, highly contradictory data in the literature on the action of K^+ and Na^+ ions on the duration of the preautomatic pause. If it is remembered that some workers [5] used only brief electrical stimulation (10-15 sec), whereas others [4, 7, 8] used only long electrical stimulation (up to 3-5 min), the reason for the discrepancy between the results of these two groups of investigations will be obvious.

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