ACTION OF Rb^+ AND Cs^+ IONS ON INHIBITION OF VENTRICULAR PACEMAKER RHYTHM BY FAST STIMULATION

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The action of Rb^+ and Cs^+ ions on the degree of inhibition of ventricular pacemaker activity by fast stimulation was investigated in experiments on the rabbit heart, isolated by Langendorf's method, with a complete artificial atrio-ventricular block. Rb^+ and Cs^+ ions were found to shorten the period of poststimulation asystole. The effect of Rb^+ and Cs^+ is not sensitive to ouabain. The reduction in the degree of inhibition of ventricular pacemaker activity by fast stimulation produced by Rb^+ and Cs^+ ions is attributed to activation of active ionic transport in the pacemaker fibers.

If a complete atrio-ventricular block is present, temporary asystole is produced as an off-response to fast electrical ventricular stimulation [4]. In its origin this poststimulation asystole is regarded as analogous to the preautomatic pause arising during acute complete atrio-ventricular block [2, 4, 5] and the periodic asystole connected with the phenomenon of self-inhibition of ventricular pacemaker activity [1, 4].

The development of poststimulation asystole has been explained by relative insufficiency of active ionic transport in the ventricular pacemaker fibers during unaccustomedly high-frequency excitation [2, 5].

Ouabain, a specific inhibitor of membrane transport ATPase, and inhibitors of energy metabolism disturbing ATP resynthesis inhibit the spontaneous ventricular pacemaker activity and lengthen the preautomatic pause [2, 3, 5, 10].

Certain procedures activating the processes of active ionic transport have been shown to shorten the period of poststimulation asystole. These procedures included an increase in the K^+ ion concentration [5]. An inverse relationship has been found between the K^+ ion concentration and the duration of poststimulation asystole. The action of K^+ ions was completely abolished by ouabain. These experiments were repeated by the present writers with the same result.

To test the hypothesis of the effect of activation of active ionic transport on the degree of inhibition of ventricular pacemaker activity by fast stimulation, a series of experiments was carried out to study the effect of Rb^+ and Cs^+ ions, which also activate membrane transport ATPase [6, 8, 9], on the heart.

EXPERIMENTAL METHOD

The test object was the rabbit's heart isolated by Langendorf's method. Oxygenated Tyrode solution of the usual composition was used for perfusion. The temperature was maintained at 36.5 ± 0.3° C.

Complete atrio-ventricular block was produced by ligating or clamping the superior part of the atrio-ventricular conducting bundle. The ECG was recorded from electrodes applied to the ventricles. After establishment of an idioventricular rhythm, the ventricles were stimulated for 3 min with supraliminal pulses of current at a frequency 2.5 times higher than the intrinsic frequency of ventricular excitation (the

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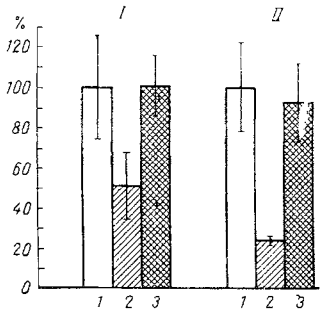

Fig. 1. Action of Rb^+ and Cs^+ ions on duration of poststimulation asystole (in % of initial value). I: 1) Initial duration of poststimulation asystole during perfusion of the heart with normal Tyrode solution (100%); 2) duration of poststimulation asystole during the action of Rb^+ ions; 3) restoration of initial duration of preautomatic pause during perfusion of the heart with normal Tyrode solution. II: 1) Initial duration of poststimulation asystole during perfusion of the heart with normal Tyrode solution (100%); 2) effect of Cs^+ ions on duration of the preautomatic pause; 3) restoration of initial duration of preautomatic pause during perfusion of the heart with normal Tyrode solution.

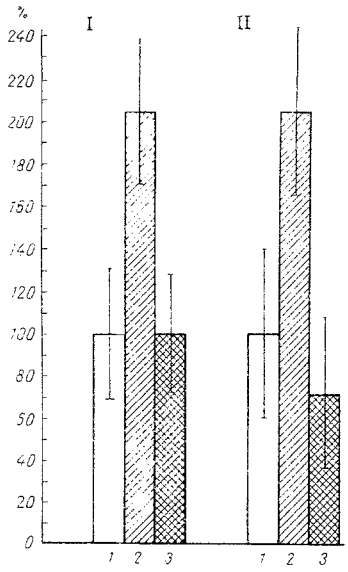

Fig. 2. Action of Rb^+ and Cs^+ ions on the heart poisoned with K-strophanthin-β (in % of initial value). I: 1) Initial duration of poststimulation asystole during perfusion of the heart with normal Tyrode solution (100%); 2) increase in duration of preautomatic pause under the influence of K-strophanthin-β; 3) shortening of poststimulation asystole by the action of Rb^+ ions. II: 1) Initial preautomatic pause during perfusion with normal Tyrode solution (100%); 2) increase in duration of preautomatic pause under the influence of K-strophanthin-β; 3) shortening of poststimulation asystole by the action of Cs^+ ions.

frequency of excitation was counted before each period of stimulation). To determine the initial value of the poststimulation asystole its duration was measured during perfusion with a solution containing Rb^+ or Cs^+ ions and during subsequent perfusion with Tyrode solution of unchanged composition.

EXPERIMENTAL RESULTS

According to data in the literature [8] K is 20% more active than Rb and 4-5 times more active than Cs in activating membrane transport ATPase, or the ratio between the activities of K : Rb : Cs is 1 : 0.84 : 0.22.

The addition of RbCl (0.1-1.5 mM) or CsCl (1-5 mM) to the Tyrode solution had no significant effect on the duration of poststimulation asystole.

Under the influence of RbCl in a concentration of 2 mM (9 experiments), the initial duration of poststimulation asystole (mean 24 sec) was approximately halved (to 50.3% of the initial value, $P < 0.001$). During subsequent perfusion of the heart with Tyrode solution of unchanged composition the duration of poststimulation asystole returned to its initial level (to 100.4%, $P < 0.01$; Fig. 1). RbCl in a concentration of 2 mM reduced the frequency of spontaneous ventricular excitation on the average by 52% ($P < 0.001$).

Under the influence of CsCl in a concentration of 10 mM (5 experiments), the initial duration of poststimulation asystole was reduced almost fourfold (to 23.1% of the initial value, $P < 0.01$). During subsequent perfusion of the heart with normal Tyrode solution the duration of poststimulation asystole was again increased almost to its initial level (to 92.9%, $P < 0.01$; Fig. 1). CsCl in a concentration of 10 mM had no significant effect on the frequency of idioventricular excitation.

The effective concentrations of Rb and Cs thus established were close to the concentrations required for semimaximal activation of membrane transport ATPase. Experiments carried out on the crab nerve have shown that this concentration is 1.8 mM for Rb and 8.0 mM for Cs [9].

The action of effective concentrations of Rb and Cs was tested in a series of experiments on the heart poisoned with strophanthin. The preparation K-strophanthin-β, produced at the Institute of Chemistry of Plant Substances, Academy of Sciences of the Uzbek SSR (molecular weight 728), analogous to ouabain, when used in a concentration of $1.4 \cdot 10^{-7}$ M doubled the duration of poststimulation asystole (to 204% of the initial level, $P < 0.001$; Fig. 2) and increased the frequency of spontaneous excitation of the ventricles on the average by 28% ($P < 0.01$).

The duration of poststimulation asystole, when increased by strophanthin, was again restored to its initial level by the action of Rb (9 experiments, $P < 0.001$; Fig. 2), and by the action of Cs ions (8 experiments) it was reduced to 71.5% of the initial level ($P < 0.001$; Fig. 2). The frequency of ventricular excitation was reduced by 68 ($P < 0.001$) and 89% ($P < 0.001$) respectively.

The results show that Rb^+ and Cs^+ ions, which increase the activity of membrane transport ATPase, reduce the poststimulation inhibition of ventricular pacemaker activity. The action of Rb and Cs on the duration of poststimulation asystole was identical, allowing for the gradient and activity. These results can be regarded as confirmation of the view that the inhibition of ventricular pacemaker activity by high-frequency stimulation is connected with the state of active ionic transport and the activity of membrane transport ATPase.

The fact that Rb^+ and Cs^+ ions continue to act even after poisoning of the heart by strophanthin was unexpected. Since ouabain abolishes the activating action of these ions on ATPase [7], it might be expected that they would not act on the poisoned heart. This expectation would be increased because K-strophanthin-β, both in Saidkarimov's [5] and our own experiments, abolished the action of K^+ ions on the duration of poststimulation asystole. The possible explanation of this fact is that we used much lower concentrations of ouabain than those which abolished the action of Rb and Cs in the experiments on the squid axon [7]. However, those concentrations (10^{-5}–10^{-4} M) could not be used on the heart because of their high toxicity.

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