ACTION OF MANGANESE IONS ON AUTOMATIC ACTIVITY OF MYOCARDIAL FIBERS INDUCED BY NICKEL IONS

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Automatic electrical activity of the myocardial fibers was evoked by keeping a strip of myocardium from the frog ventricle for 5-8 h in Ringer's solution containing $NiCl_2 \cdot 6H_2O$ in a concentration of 4-5 mM. Next, $MnCl_2 \cdot 4H_2O$ was added to this solution in a concentration of 1-10 mM. Under the influence of Mn^{++} ions in concentrations of 1-5 mM in 70% of experiments the automatic activity was abolished in the course of 1-2 min. In the remaining experiments the automatic activity lasted 3-30 min, but in the course of time it became irregular and then disappeared altogether. With concentrations of Mn^{++} ions of 6-10 mM automatic activity disappeared in 83% of experiments in the first 1-2 min, and in the rest it lasted 3-25 min. After the disappearance of the automatic activity in all cases in response to a single electric pulse secondary discharges appeared; their number varied from one to several dozens; i.e., the effect of the Ni^{++} ions still continued to some extent. It is postulated that the reason for this partial preservation of the effect of Ni^{++} ions after the action of Mn^{++} ions is that these ions are antagonistists with respect to their action on the slow sodium–calcium current.

KEY WORDS: myocardium; automatic activity; manganese ions.

Facts indicating that Mn^{++} and Ni^{++} ions act antagonistically on the excitable membrane of the myocardial fiber were the starting point of this investigation. Ni^{++} ions lengthen the plateau of the action potential (AP), increase the second (slower than the first) phase of initial depolarization and overshoot, and evoke an automatic activity of the myocardial fibers of the frog ventrical that is not usually observed [3, 4]. Mn^{++} ions shorten the AP plateau, reduce the second phase of initial depolarization [6-9], and depress the automatic activity of the sinus node of the frog [2] and the sino-atrial node of mammals [10, 11] and also the automatic activity of the myocardial fibers of the frog ventrical evoked by Ba^{++} ions and by certain other changes in the ionic composition of the medium [1]. The action of Mn^{++} ions on the electrical activity of the myocardial fibers is explained on the grounds that they depress the slow sodium–calcium current (block the sodium–calcium channel) responsible for the appearance of the AP plateau [8, 9] and for the development of slow diastolic depolarization [1]. Considering that Ni^{++} ions induce changes opposite to Mn^{++} ions in the electrical activity of the myocardial fibers, they presumably must activate the slow sodium–calcium current. The antagonistic action of Mn^{++} and Ni^{++} ions was manifested clearly during their consecutive action on a strip of myocardium from the frog ventricle [5]. The AP plateau, lengthened under the influence of Ni^{++} ions, was shortened somewhat by the action of Mn^{++} ions, and the AP plateau shortened by Mn^{++} ions was lengthened by the subsequent action of Ni^{++} ions.

The next step in the study of this problem was to investigate the action of Mn^{++} ions on the automatic activity of the myocardial fibers evoked by Ni^{++} ions.

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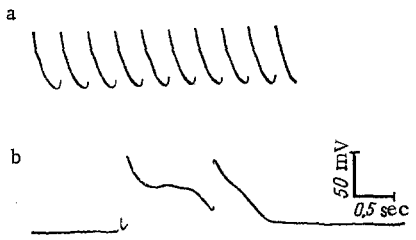

Fig. 1

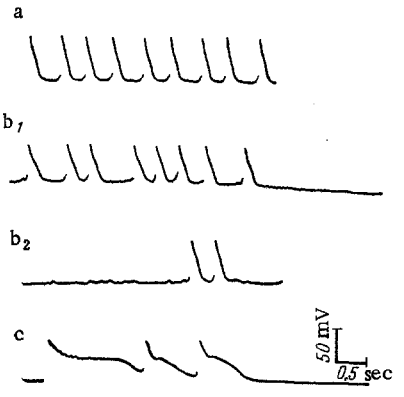

Fig. 2

Fig. 1. Effect of Mn^{++} ions on automatic activity of myocardial fibers of the frog ventricle evoked by Ni^{++} ions: a) automatic activity with a frequency of 170/min arising 8 h after immersion of myocardium in Ringer's solution containing 4 mM $NiCl_2 \cdot 6H_2O$; b) disappearance of automatic activity after addition of 10 mM $MnCl_2 \cdot 4H_2O$ to Ringer's solution bathing the preparation and appearance of two APs in response to a single stimulus.

Fig. 2. Change evoked by Ni^{++} ions in automatic activity of myocardial fibers of the frog ventricle produced by the action of Mn^{++} ions: a) automatic activity arising 7 h after immersion of myocardium in Ringer's solution containing 4 mM $NiCl_2 \cdot 6H_2O$; b) automatic activity 1 min after addition of 4 mM $MnCl_2 \cdot 4H_2O$ to Ringer's solution containing $NiCl_2$; activity became irregular (b_2 is the direct continuation of b_1); c) disappearance of automatic activity 5 min after combined action of $NiCl_2$ and $MnCl_2$. Appearance of three APs in response to a single stimulus.

EXPERIMENTAL METHOD

Altogether 23 experiments were carried out on strips of myocardium from the frog ventricle. The strips were 3-5 mm long and 1.5-2 mm wide. APs were recorded by glass microelectrodes with a tip 0.5 μ in diameter and filled with 3 M KCl solution. Ringer's solution of the following composition (in mM) was used: NaCl 110.5, KCl 2.5, $CaCl_2$ 1.8, $NaHCO_3$ 2.4; $NiCl_2 \cdot 6H_2O$ was used in a concentration of 4-5 mM, and $MnCl_2 \cdot 4H_2O$ in a concentration of 1-10 mM. The pH of the solutions was 7.3-7.4.

EXPERIMENTAL RESULTS

The automatic electrical activity of the myocardial fibers was evoked by keeping the preparation for 5-8 h in Ringer's solution containing $NiCl_2 \cdot 6H_2O$ in a concentration of 4-5 mM (Figs. 1a and 2a). After the automatic activity had become regular and stable, the Ringer's solution was changed for a similar solution to which $MnCl_2 \cdot 6H_2O$ had been added in concentrations of 1-10 mM. Under the influence of Mn^{++} ions in concentrations of 1-5 mM the automatic activity was abolished in 70% of the experiments in the course of 1-2 min. In the remaining 30% of the experiments the automatic activity persisted for 3-30 min, but in the course of time it became irregular and it disappeared completely (Fig. 2b, c). In response to stimulation by a single pulse repeated discharges appeared in both cases; their number varied from one to several dozens (Figs. 1b and 2c). With higher concentrations (6-10 mM) in 83% of cases the automatic activity disappeared during the first 1-2 min (Fig. 1b), and in 17% it persisted for 3-25 min.

These experiments showed that Mn^{++} ions depress the automatic activity evoked by Ni^{++} ions. However, they did not depress the ability of the myocardial fibers to discharge automatically as quickly and completely as Mn^{++} ions depressed the natural automatic activity of the frog's sinus node or the automatic activity induced by Ba^{++} ions, or by the exclusion of K^+ and Ca^{++} ions from the Ringer's solution, or by the addition of tetraethylammonium chloride (TEA) or ethylenediaminetetraacetate (EDTA) to the Ringer's solution [1]. This indicates that the effects of Ni^{++} are not completely abolished by Mn^{++} ions. The results

of these experiments are in agreement with those of previous investigations [11] showing that Mn^{++} ions do not abolish the AP plateau when lengthened by Ni^{++} ions but only shorten it to some extent.

As already stated, the effects evoked by Mn^{++} ions (shortening of the AP plateau and abolition of automatic activity) can be explained on the grounds that these ions depress the slow sodium–calcium current [1, 6-9]. Accordingly, the fact of the partial preservation of the effects produced by Ni^{++} ions after the action of Mn^{++} ions can be explained in two ways. First, it can be assumed that Ni^{++} ions increase the conductance of the slow sodium–calcium channel to such a degree that Mn^{++} ions in the concentrations used can no longer block it completely. The automatic activity and multiple responses of a strip of myocardium, kept for a long time in a solution containing $NiCl_2$ and then exposed to the action of Mn^{++} ions, to a single electrical stimulus sometimes, therefore, persist for a long time. Second, it can be postulated that Ni^{++} ions act not only by activating the slow sodium–calcium current, but also by modifying some other process in the membrane of the myocardial fibers on which manganese ions have no appreciable action. This process could be lowering the potassium conductance of the membrane.

To test the validity of the second explanation, experiments were carried out with combined exposure to Ni^{++} ions and TEA, which delays the potassium conductance of the membrane. If the lowering of potassium conductance plays a role in the action of Ni^{++} ions, during the simultaneous action of Ni^{++} ions and TEA the APs ought to be lengthened. However, combined exposure to $NiCl_2$ in a concentration of 4 mM and TEA in a concentration of 15 mM led to lengthening of the AP by about the same extent as exposure to $NiCl_2$ only. This fact is interpreted as evidence that the lengthening of the AP plateau under the influence of Ni^{++} ions is not connected with a lowering of the potassium conductance of the membrane. The hypothesis that the partially preserved effects of Ni^{++} ions after treatment with Mn^{++} ions can be explained by a delayed increase in the potassium conductance of the membrane was thus not confirmed in these experiments. It is therefore considered that the first of the possible explanations of the fact that Mn^{++} ions do not always abolish the effects of Ni^{++} ions quickly and completely is more correct. The experiments described above suggest that Ni^{++} ions are activators of the sodium–calcium current and that this explains the changes induced by them in the electrical activity and automatic excitation of the myocardial fibers.

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