ELECTRICAL AND MECHANICAL RESPONSES TO DILTIAZEM IN POTASSIUM DEPOLARIZED MYOCARDIUM OF THE GUINEA PIG

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Abstract—Effects of diltiazem on the electrical and mechanical activities of guinea pig papillary muscle were investigated in K-rich Tyrode's solution (KCl 12.7 mM). The electrical properties of cell membrane in K-rich solution were also examined in the ventricular muscle fibers. It was found that the overshoot as well as the maximum rate of rise (V_{max}) of the action potential were highly sensitive to the extracellular concentration of CaCl_2 in K-rich solution. V_{max} was also affected by NaCl. Diltiazem at a lower concentration (1.1 \times 10^{-7} M) caused a reduction in the contractile force of K-depolarized papillary muscle without producing significant changes in the resting and action potentials. In the presence of a higher concentration of diltiazem (1.1 \times 10^{-5} M), the contractile force decreased concurrently with the change in the action potential. Addition of CaCl_2 restored the original strength of contraction in parallel to the recovery of the action potential, especially in its overshoot and V_{max}. From these results, it is inferred that diltiazem may decrease the contractile force of guinea pig papillary muscle either by interfering with the transmembrane calcium influx or by intracellularly reducing the free calcium ion concentration in the myoplasm.

In previous experiments carried out in normal Tyrode's solution (KCl 2.7 mM) (1), it was shown that diltiazem (CRD-401), a new 1,5-benzothiazepine derivative (2) with a potent coronary vasodilating activity (3), has a property which interferes with the excitation-contraction coupling in the isolated guinea pig myocardium. It was also suggested that the compound antagonizes calcium ion essential for muscle contraction, thus causing a reduction in the contractile force of the myocardium (1). On the other hand, it has been reported that the slow inward calcium or calcium-sodium current, as well as the fast inward sodium current, is involved in the generation of the action potential of cardiac muscle fibers under normal physiological conditions (4-13). The slow inward calcium current, which is assumed to play an important role in the excitation-contraction coupling in the cardiac muscle (8, 12, 14-19), is disclosed as a result of the inactivation of sodium carrying system when the extracellular concentration of KCl was increased (20-23). Therefore, the present experiments carried out in K-rich Tyrode's solution (KCl 12.7 mM) were an attempt to analyze further the calcium-antagonistic property of the compound in the isolated guinea pig myocardium. The electrical properties of cell membrane of guinea pig ventricular

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Muscle fibers in K-rich solution were also examined.

MATERIALS AND METHODS

Isolated papillary or ventricular muscle of the guinea pig was used. The experimental procedures were similar to those described in the previous papers (1, 13). Membrane depolarization was induced by adding 1 M KCl solution (0.1 ml) to the organ bath containing normal Tyrode’s solution (10 ml, KCl 2.7 mM). The final concentration of KCl in the solution was 12.7 mM. After the membrane potential or contractile force attained equilibrium in K-rich Tyrode’s solution, 0.1 ml of the test compound solution was added to the organ bath to give a final concentration. When the concentration of NaCl was changed, NaCl was substituted by osmotically equivalent sucrose solution. In each series of experiments, transmembrane action potential was recorded from the same cell during the period of observation. The preparation was driven by the rectangular current pulse (5 msec in duration, about twice the threshold) applied extracellularly at a constant rate (1.3 Hz) through a pair of Ag-AgCl electrodes. The composition of normal Tyrode’s solution was as follows (mM): NaCl 136.8, KCl 2.7, CaCl₂ 1.8, MgCl₂ 0.49, glucose 5.6, Tris-HCl buffer 5.4 (pH 7.2). All experiments were carried out at 30±0.5°C. The chemical structure of diltiazem is shown in Fig. 1.

RESULTS

Action potentials of ventricular muscle fibers in K-rich Tyrode’s solution

Effect of KCl: When the concentration of KCl in normal Tyrode’s solution was increased from 2.7 to 12.7 mM, the resting potential changed from -88.6±0.9 to -62.6±0.6

| Concentration (mM) | R.P. (mV) | A.P. (mV) | O.S. (mV) | Vmax (V/sec) | Duration of A.P. (msec) |
|--------------------|-----------|-----------|-----------|--------------|------------------------|
| 2.7                | 88.6±0.9  | 122.9±1.4 | 34.3±0.8  | 155.9±7.7    | 246.7±5.4              |
| 12.7               | 62.6±0.6* | 89.1±1.5* | 26.5±1.2* | 56.7±4.9*    | 184.8±7.5*             |

Values were obtained 10 min after the concentration of KCl was increased from 2.7 to 12.7 mM. Each value is the mean±SE of 20 experiments. R.P., resting potential; A.P., amplitude of the action potential; O.S., overshoot; Vmax, maximum rate of rise of the action potential; duration of A.P., duration of the action potential measured at 50% and 90% repolarization. Significant difference (paired t-test); *P<0.01.
mV (mean±SE of 20 experiments) 10 min after the increase in KCl concentration (Fig. 2 and Table 1). The overshoot and maximum rate of rise (V_{max}) of the action potential were reduced, while the duration of action potential measured at either 50% or 90% repolarization was shortened. It was also observed in Fig. 2 that the latter part of upstroke of the action potential rose more slowly than in normal Tyrode’s solution.

**Effect of CaCl₂**: Fig. 3 shows the effect of extracellular concentration of CaCl₂ on the intracellularly recorded resting and action potentials in K-rich solution. The concentration of NaCl was kept at 136.8 mM. It was evident that the overshoot increased remarkably when the concentration of CaCl₂ was changed from 1.8 to 7.8 mM: regression analysis gave a slope of 26.9±1.2 mV (mean±SE of 10 experiments) for a 10-fold change in CaCl₂ concentration. This value was close to that predicted by the Nernst equation for a membrane selectively permeable to calcium ions (30 mV/decade at 30°C). As shown in Fig. 3, V_{max} was also considerably enhanced by increasing CaCl₂ concentration. On the other hand, changes in the duration of the action potential were not proportional to the extracellular concentration of CaCl₂. There was no significant change in the resting potential. Similar results were also obtained when stimulus of a low frequency (0.2 Hz) was applied to the preparation at CaCl₂ concentration ranging from 0.6 to 7.8 mM.

**Effect of NaCl**: Fig. 4 represents experimental results in which the concentration of NaCl in K-rich solution was decreased from 136.8 to 50 mM in the presence of 1.8 mM CaCl₂. Sometimes different shapes (amplitude, duration) of the action potential appeared alternately, when muscles were driven at 1.3 Hz in a lower concentration of NaCl. Thus, stimulus of a low frequency (0.2 Hz) was used in the present experiments to obtain the constant response. As shown in Fig. 4, the change in overshoot in response to the extracellular concentration of NaCl was slight. Regression analysis indicated that the overshoot varied 7.4±0.7 mV (mean±SE of 9 experiments) for a 10-fold change in NaCl concentration, the value of which being approx. one-eighth of that predicted by the Nernst equation (60 mV/decade at 30°C). On the other hand, a marked decrease in V_{max} and a shortening of the duration of action potential were observed as the concentration of NaCl was decreased from 136.8 to 50 mM. The resting potential was not affected significantly.
FIG. 3. Effect of CaCl₂ on the intracellularly recorded resting and action potentials of ventricular muscle fibers in K-rich Tyrode’s solution. The concentration of NaCl was kept at 136.8 mM. CaCl₂ was added cumulatively to the preparation. A: An example of the experimental record. Each photo was taken 5 min after addition of CaCl₂. Time calibration for the record of fast sweep speed is shown in the bottom of the photo. Time marks in 10 (small pips) and 50 msec (large pips) intervals. B: Relation between transmembrane potential and extracellular concentration of CaCl₂. O.S., overshoot; APD₅₀ and APD₉₀, duration of the action potential measured at 50% and 90% repolarization, respectively; Vₘₐₓₓ, maximum rate of rise of the action potential; R.P., resting potential. Values were taken 5–10 min after addition of CaCl₂. Each point is the mean±SE of 10 experiments. Significant difference (paired t-test) between control (CaCl₂ 1.8 mM) and experiment; †P<0.05, *P<0.01.

FIG. 4. Effect of NaCl on the intracellularly recorded resting and action potentials of ventricular muscle fibers in K-rich Tyrode’s solution. The concentration of CaCl₂ was kept at 1.8 mM. Records were taken after the action potential attained an equilibration in each concentration of NaCl. Preparations were stimulated at a rate of 0.2 Hz. A: An example of the experimental record. B: Relation between transmembrane potential and extracellular concentration of NaCl. Each point is the mean±SE of 9 experiments. Significant difference (paired t-test) between control (NaCl 136.8 mM) and experiment; †P<0.05, *P<0.01. Other explanations are similar to those described in Fig. 3.
Effect of diltiazem in K-rich Tyrode's solution

Contractile force of papillary muscle: Increase in KCl concentration from 2.7 to 12.7 mM produced a decrease in the contractile force of the isolated papillary muscle. In some preparations, this decrease was followed by a slight increase. In any case, 10 min after the increase in KCl concentration, the contractile force attained an almost equilibration, being 68.5 ± 2.5% of the control (mean ± SE of 40 experiments).

When diltiazem was added to the K-depolarized papillary muscle, the contractile force decreased dose-dependently (Fig. 5, Table 2). The decrease in the contractile force in K-rich Tyrode's solution (KCl 12.7 mM) was more marked than in normal Tyrode's solution (KCl 2.7 mM) (cf. 1). For example, the concentrations of diltiazem which reduced the contractile force to approx. 69% of the control were 1.1 × 10⁻⁵ and 1.1 × 10⁻⁷ M in normal and K-rich solutions, respectively. Fig. 5 shows the antagonistic relation between diltiazem and CaCl₂ on the contractile force. Table 2 summarizes the results. The contractile force

![Fig. 5. Effects of diltiazem and CaCl₂ on the contractile force of K-depolarized papillary muscle. Initial concentration of CaCl₂ was 1.8 mM. CaCl₂ was added 10 min after addition of diltiazem. Arrows in the figure represent the concentration of CaCl₂ (mM) necessary for restoring the original strength of contraction. Each point is the mean ± SE of 10 experiments.](image)

**Table 2.** Antagonistic relation between diltiazem and CaCl₂ on the contractile force of K-depolarized papillary muscle

| Conc. of diltiazem (M) | Contractile force (% of control) | Compensatory conc. of CaCl₂* (mM) | Molar ratio (diltiazem : CaCl₂) |
|------------------------|----------------------------------|------------------------------------|-------------------------------|
| 4.4 × 10⁻⁴             | 83.8 ± 3.3                       | 0.18                               | 1 : 4091                      |
| 1.1 × 10⁻⁷             | 68.2 ± 3.9                       | 0.36                               | 1 : 3273                      |
| 2.2 × 10⁻⁷             | 56.2 ± 2.2                       | 0.62                               | 1 : 2818                      |
| 1.1 × 10⁻⁶             | 37.1 ± 3.2                       | 1.15                               | 1 : 1045                      |
| 1.1 × 10⁻⁵             | 11.6 ± 1.7                       | 3.05                               | 1 : 277                       |

Molar ratio of diltiazem to CaCl₂ was calculated from 1st and 3rd columns. Mean values of 10 experiments. * Concentration of CaCl₂ necessary for restoring the original strength of contraction.
reduced by diltiazem was antagonized with the increase in extracellular concentration of CaCl₂ and the original strength of contraction was thus restored. In Fig. 5, the concentration of CaCl₂ necessary for restoring the original contractile force was calculated (indicated by arrows in the figure), and such was not proportional to the concentration of diltiazem. As summarized in Table 2, the antagonistic ratio of diltiazem to calcium ions was estimated to be approx. 1:300-4,000 in the concentration range of diltiazem from 1.1 × 10⁻⁵ to 4.4 × 10⁻⁸M.

Transmembrane resting and action potentials of ventricular muscle fibers: Results are shown in Fig. 6 and Table 3. In K-rich Tyrode's solution, a lower concentration of diltiazem (1.1 × 10⁻⁷ M) produced no significant influence on the resting and action potentials. At 1.1 × 10⁻⁶ M diltiazem, only a slight reduction of Vₘₐₓ was observed. On the other hand, various parameters of the action potential were affected by a higher concentration of diltiazem (1.1 × 10⁻⁵ M): the overshoot and Vₘₐₓ were reduced and the duration of action potential was shortened at either 50% or 90% repolarization. There was no significant change in the resting potential. These effects of diltiazem on the action potential were reversed after removing the compound (Fig. 6).

As in the case of contractile response of the papillary muscle, the effect of diltiazem on the action potential was antagonized with the increase in extracellular concentration of CaCl₂. As shown in Table 3, the overshoot and Vₘₐₓ reduced by 1.1 × 10⁻⁵ M diltiazem recovered completely after addition of CaCl₂ in the concentration range from 2 to 6 mM. The duration of action potential measured at 90% repolarization was restored to its original value when a higher concentration of CaCl₂ (11 mM) was added to the preparation. On the other hand, the duration measured at 50% repolarization showed a tendency to recover as the extracellular concentration of CaCl₂ was increased.

Simultaneous measurements of contractile force and transmembrane action potential of papillary muscle: Figs. 7 and 8 represent the effects of diltiazem on the contractile force measured simultaneously with the resting and action potentials in K-rich Tyrode's solution. As shown in Fig. 7, diltiazem at a lower concentration (1.1 × 10⁻⁷ M) reduced the contractile force by approx. 40% of the control 30 min after addition of the compound, whereas no significant change was discernible in the resting and action potentials. Addition of CaCl₂ (0.4 mM) to the preparation exposed to diltiazem restored the original strength of contraction. On the other hand, in the presence of a higher concentration of diltiazem (1.1 × 10⁻⁵ M), the contractile force decreased concurrently with change in the action potential (Fig. 8).
|               | No. of Expts. | R.P. (mV) | A.P. (mV) | O.S. (mV) | $V_{\text{max}}$ (V/sec) | Duration of A.P. (msec) 50% | Duration of A.P. 90% |
|---------------|---------------|-----------|-----------|-----------|-------------------------|-----------------------------|------------------------|
| Control       | 10            | 63.2 ± 1.0| 90.1 ± 1.3| 26.9 ± 1.3| 48.5 ± 3.9              | 171.9 ± 10.8                | 195.2 ± 12.7            |
| $1.1 \times 10^{-7}$ M |              | 63.6 ± 1.1| 90.6 ± 1.3| 27.0 ± 1.4| 48.6 ± 4.1              | 171.0 ± 10.7                | 194.4 ± 12.5            |
| Control       | 8             | 63.0 ± 0.6| 91.8 ± 1.2| 28.8 ± 1.1| 62.5 ± 7.1              | 168.1 ± 10.6                | 195.8 ± 9.6             |
| $1.1 \times 10^{-6}$ M |          | 63.0 ± 0.6| 91.6 ± 1.3| 28.6 ± 1.3| 55.4 ± 6.4*             | 168.1 ± 8.3                 | 192.3 ± 8.3             |
| Control       |               | 63.7 ± 0.8| 93.3 ± 1.8| 29.6 ± 1.4| 49.7 ± 4.7              | 160.6 ± 7.6                 | 182.7 ± 11.0            |
| $1.1 \times 10^{-5}$ M |          | 62.7 ± 1.1| 79.3 ± 2.6**| 16.6 ± 2.1**| 28.3 ± 6.2**             | 125.0 ± 9.8**               | 141.3 ± 11.1**          |
| CaCl$_2$ added | 7             |           |           |           |                         |                             |                        |
| 2.0 mM        |               | 63.3 ± 0.9| 87.4 ± 3.1| 24.1 ± 2.5| 36.9 ± 6.0†              | 134.0 ± 7.2†                | 152.0 ± 8.7†            |
| 6.0 mM        |               | 63.7 ± 0.9| 102.0 ± 3.0‡ | 38.3 ± 2.3‡ | 54.4 ± 5.1              | 143.9 ± 7.1                 | 168.1 ± 8.2             |
| 11.0 mM       |               | 64.3 ± 0.6| 109.6 ± 1.9‡ | 45.3 ± 1.9‡ | 63.3 ± 3.8‡             | 148.9 ± 8.1                 | 181.0 ± 10.0            |

Values were obtained 10 min after addition of diltiazem. In the presence of $1.1 \times 10^{-5}$ M diltiazem, CaCl$_2$ was added cumulatively and records were taken 5–10 min intervals. Initial concentration of CaCl$_2$ was 1.8 mM. Abbreviations are as in Table 1. Significant difference (paired t-test) between control and diltiazem, * P < 0.1, ** P < 0.01; between control and CaCl$_2$, † P < 0.05, ‡ P < 0.01.
Fig. 7. Simultaneous recordings of the transmembrane potential and contractile force of K-depolarized papillary muscle in the presence of $1.1 \times 10^{-7}$ M diltiazem. A: An example of the experimental record. Each trace (top to bottom) shows zero voltage, action potential, contractile force and differentiation curve of the action potential ($V_{\text{max}}$). B: Time courses for the effect of diltiazem. • contractile force (C.F.); ○ ○ ○, resting potential (R.P.); △△△△, overshoot (O.S.); ● ● ●, maximum rate of rise of the action potential ($V_{\text{max}}$). ■ ■ ■, duration of the action potential at 50% repolarization (APD_{50}); □ □ □, duration of the action potential at 90% repolarization (APD_{90}). CaCl$_2$ (0.4 mM) was added 30 min after addition of diltiazem. Mean values of 3 experiments.

Fig. 8. Simultaneous recordings of the transmembrane potential and contractile force of K-depolarized papillary muscle in the presence of $1.1 \times 10^{-5}$ M diltiazem. Explanations are similar to those described in Fig. 7. CaCl$_2$ (4 mM) was added 30 min after addition of diltiazem. Mean values of 5 experiments.

There was no significant change in the resting potential. As shown in Fig. 8, the contractile force was approx. 10% of the control 30 min after addition of diltiazem. When CaCl$_2$ (4 mM) was added, the contractile force completely regained the original strength in parallel to the recovery of the action potential, particularly in the overshoot and $V_{\text{max}}$. 
DISCUSSION

The action potential of K-depolarized ventricular muscle fibers (dog and cat, KCl 13.5 or 18.9 mM) has been interpreted by Mascher (20, 21) as follows: the initial rising phase preceding the slow regenerative response is attributed to an increase in the membrane conductance to sodium ions, while an increase in the membrane conductance to calcium ions plays an important role in the genesis of the slow regenerative response. According to Tritthart et al (22) and Weiss et al (23) the action potential of cat papillary muscle is mediated by the slow inward calcium current in K-rich solution (KCl 13.7 mM).

In the present experiments, the following results were obtained on the action potential of guinea pig ventricular muscle fibers bathed in K-rich Tyrode's solution (KCl 12.7 mM).

1. The slope of the relation between overshoot and extracellular concentration of CaCl$_2$ approximated the expected value for the membrane selectively permeable to calcium ion. On the contrary, the change in overshoot in response to the NaCl concentration was slight and only one-eighth of that predicted by the Nernst equation. 2. $V_{\text{max}}$ depended upon the extracellular concentration of CaCl$_2$ as well as NaCl. In addition to these findings, it was also observed that the action potential was almost abolished in nominally calcium-free K-rich solution containing normal concentration of NaCl (136.8 mM). On the other hand, it has been shown that in normal Tyrode's solution (KCl 2.7 mM), the overshoot and $V_{\text{max}}$ were less sensitive to the extracellular concentration of CaCl$_2$, while the action potential could be evoked in a calcium-free solution when NaCl (136.8 mM) was present (13). Therefore, it is assumed that in contrast to the action potential in normal Tyrode's solution, the action potential of guinea pig ventricular muscle fibers in K-rich Tyrode's solution is largely calcium-dependent and that calcium ion contributes considerably to the height of the action potential, although the inward current during the rising phase of the action potential is possibly carried by both calcium and sodium ions.

In K-rich Tyrode's solution, diltiazem decreased the contractile force of the isolated guinea pig papillary muscle. This effect was antagonized with increase in the extracellular concentration of CaCl$_2$. Changes in the transmembrane action potential of the ventricular muscle fibers caused by diltiazem were also reversed by the addition of CaCl$_2$. Simultaneous measurements of the contractile force and transmembrane action potential of K-depolarized papillary muscle indicated that a higher concentration of diltiazem (1.1 x 10$^{-5}$ M) decreased the contractile force concurrently with the change in the action potential. Namely, the overshoot and $V_{\text{max}}$ were reduced and the duration of action potential was shortened, while the resting potential was unchanged. Addition of CaCl$_2$ restored the original strength of contraction in parallel to the recovery of the action potential, especially in its overshoot and $V_{\text{max}}$. Since the action potential in K-rich Tyrode's solution is assumed to depend mainly upon the extracellular concentration of calcium ion as mentioned above, the results suggest that a reduction of the transmembrane calcium influx into the cell may be responsible for the decrease in the contractile force caused by diltiazem.

On the other hand, a lower concentration of diltiazem (1.1 x 10$^{-7}$ M) produced a decrease in the contractile force of K-depolarized papillary muscle without affecting significantly
the resting and action potentials, suggesting that the compound has a property which interferes with the excitation-contraction coupling in the cardiac muscle. Therefore, it may also be possible that diltiazem in some way reduces intracellularly the free calcium ion concentration available for the contractile system, thus causing a decrease in the contractile force. A reduction of free calcium ion concentration may be ascribed to the inhibition of a certain calcium-releasing mechanism inside the cell, although an acceleration of calcium-uptake mechanism cannot be ruled out. Recently, it has been reported for both skeletal (24–26) and cardiac muscles (27–29) that a small amount of calcium ion triggers a regenerative release of calcium ion which activates the contractile system. Thus, inhibition of such a calcium-induced calcium-releasing mechanism may be involved in the inhibitory effect of diltiazem on the contractile force.

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