Extracellular Potassium Dependent Negative Dromotropic Action of Nicorandil in Guinea Pig Myocardium

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Extracellular Potassium Dependent Negative Dromotropic
Action of Nicorandil in Guinea Pig Myocardium

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Abstract Although the antiarrhythmic action of nicorandil is drawing an increasing
attention, dromotropic effect of this agent is unclear. Therefore, this was investigated by
microelectrode technique to the superfused guinea pig papillary muscle to record the
action potential and extracellular potential during conduction. The correlation of
myocardial internal longitudinal resistance (r₁) assumed to reflect the global gap junctu-
nal resistance, maximum rate of rise of the action potential upstroke (Vₘₐₓ), and
conduction velocity was examined under the alterations of external potassium concentra-
tions ([K⁺]ₑ; ranging from 3.0 to 12.0 mM) in the presence or absence of 100 µM
nicorandil. In the minimum [K⁺]ₑ, nicorandil caused significant (p < 0.05) hyperpolariza-
tion and reduction in Vₘₐₓ. Negative dromotropic action of nicorandil was slight but
significant (p < 0.05) in low (3.0 mM) [K⁺]ₑ but was not evident in physiologic (5.4 mM)
or elevated (9.0 to 12.0 mM)[K⁺]ₑ. In conclusion, nicorandil exerts negative dromotropic
action as [K⁺]ₑ decreased, which was accounted for by the cable analysis and may
contribute to the prevention of low [K⁺]ₑ-induced arrhythmia.

Key words: Cable theory, Conduction, Myocardium, Nicorandil, Potassium

Introduction

Myocardial electrical propagation is
modulated by various antiarrhythmic
agents in a complicated manner. As a re-
presentative example, class I antiarrhythmic
agents slow the conduction by suppressing
the fast inward sodium current (Iₕ) in a rate– and voltage-dependent manner⁴⁻⁵. Indi-
vidual class III agent shows the compli-
cated dromotropic actions⁴. A representa-
tive class IV agent, verapamil, exerts nega-
tive dromotropic action by inhibiting Iₕ at
relatively higher concentrations (> 1.0 µM)
in aerobic condition, whereas this agent
shows positive dromotropism by restoring
cell-to-cell uncoupling at a concentration
of 1.0 µM under the anaerobic condition⁶. Ouabain, not classified by the Vaughan-
Williams antiarrhythmic drugs classification⁷, also exerts negative dromotropism
possibly by elevating intracellular calcium
concentration leading to cell-to-cell uncou-
pling⁷. Contrary to such a line of evidence
with respect to the drug-induced
dromotropic alterations based on the cable
theory including cell-to-cell coupling con-
cept, the dromotropic action of nicorandil,
N-(2-hydroxyethyl)-nicotinamide nitrate, is
unknown. Nicorandil shows hybrid prop-
Dromotropic effects of nicorandil

Properties as a nitrate and an adenosine triphosphate (ATP)-sensitive potassium (K\textsubscript{ATP}) channel opener. Therefore, this study was designed to investigate the dromotropic actions of nicorandil using guinea pig papillary muscles in which cable theory is apparently applicable.

Materials and Methods

Heart preparations

Experimental designs and procedures of this study compiled strictly with the Guiding Principles for the Care and Use of Laboratory Animals approved by The Japanese Physiological Society and experimental methods have been introduced elsewhere in detail. In brief, guinea pig weighing 300 to 350 g (Kyudo Co. Ltd., Yoshitomi, Japan) was anesthetized with an intraperitoneal injection of sodium pentobarbital (30-40 mg / kg; Abbott Laboratory, Chicago, IL). Beating heart was excised immediately after thoracotomy and then rinsed in ice-cold normal Tyrode's solution. This solution was of the following composition (in mM / L): NaCl, 140.0; KCl, 5.4; CaCl\textsubscript{2}, 1.8; MgCl\textsubscript{2}, 0.5; NaH\textsubscript{2}PO\textsubscript{4}, 0.33; glucose, 5.5. The external K\textsuperscript{+} concentration ([K\textsuperscript{+}]\textsubscript{e}) was elevated up to 12.0 mM or lowered to 3.0 mM, depending on the experimental protocol. In the case of [K\textsuperscript{+}]\textsubscript{e} alteration, NaCl was substituted for by KCl or vice versa to keep the total ionic strength of all kinds of solution constant. Solution was oxygenated with 100 % O\textsubscript{2} and the temperature was maintained at 36.0 ± 1.0°C. The pH was adjusted to 7.4 using 10.0 mM N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES; Sigma Co. Ltd., St Louis, MO) with NaOH titration (~0.5 g). Partial oxygen pressure of the perfusate estimated by a blood gas analyzer (ABL 620; Radiometer, Copenhagen, Denmark) was 800 mmHg approximately. Excised right ventricular papillary muscle was mounted on a tissue chamber and covered by nylon mesh to produce the thin layer of perfusate around the preparation on which two external glass electrodes were positioned in the same longitudinal axis to record the extracellular potential during electrical propagation. A pair of tungsten wire electrodes was positioned at the cut end of the preparation for stimulation and a conventional 3M KCl-filled glass microelectrode was applied to record the propagating action potential. Preparation was superfused by oxygenated Tyrode's solution at a flow rate of 3.0 ml / min and paced with 2 msec duration and twice the end-diastolic threshold intensity at constant basic cycle length (BCL) of 1.0 sec. Extracellular potential, action potential and its first time derivative were monitored by a pen-writing recticorder (Nihon-Kohden, Tokyo, Japan) and stored on digital audiotapes using a data recorder (RD-101T PCM, TEAC, Tokyo) for off-line analyses.

Theory

The following electrophysiologic parameters were analyzed under the [K\textsuperscript{+}]\textsubscript{e} alterations, i.e., resting membrane potential (RMP), the maximum rate of rise of the action potential upstroke (V\textsubscript{max}), action potential duration at 90 % repolarization (APD), interelectrode conduction time (CT), amplitudes of extracellular and intracellular potentials (V\textsubscript{e}, V\textsubscript{i}) generated by the instantaneous potential gradient between the excited and resting myocardium at a moment of electrical propagation. Here, the amplitude of intracellular action potential recorded in the bathed preparation is the sum of V\textsubscript{i} and V\textsubscript{e}. Conduction velocity (\theta) of the action potential propagation was
calculated by dividing the interelectrode distance by CT.

Fig. 1 (upper) illustrates schematically the local circuit current (I) generated by the voltage gradient in the extracellular and intracellular domains during electrical propagation. Relation of \( V_e \), \( V_i \) and \( I \) follows Ohmic equation:

\[
V_i = I \cdot r_i \tag{1}
\]
\[
V_e = I \cdot r_e \tag{2}
\]

where \( r_i \) and \( r_e \) are the internal and external longitudinal tissue resistance per unit length. Since \( I \) is constant in the instantaneous local circuit according to the charge conservation theory\(^{11}\), dividing equation [1] by equation [2] yields,

\[
\frac{r_i}{r_e} = \frac{V_i}{V_e} \tag{3}
\]

Total longitudinal tissue resistance \( (r_{total}) \) was measured by applying subthreshold constant current to the extracellular space through the platinum wires placed at the opposite ends of the preparation. Since \( r_{total} \) is the parallel combination of \( r_i \) and \( r_e \) according to the equilibrium circuit indicated in Fig. 1 (lower), the following equation is established,

\[
\frac{1}{r_{total}} = \frac{1}{r_i} + \frac{1}{r_e} \tag{4}
\]

Based on these equations [3] and [4], the following equation is obtained\(^{10,11}\),

\[
r_i = r_{total} \left(1 + \frac{V_i}{V_e}\right) \tag{5}
\]

Major component of \( r_i \) is the gap junctional but not cytoplasmic resistance, \( r_i \) roughly reflects the uncoupling condition between the contiguous cardiac cells in the multicellular preparations.

Theoretical nonlinear fitting of the relationship between \( \hat{V}_{\text{max}} \) and RMP under the \([K^+]_e\) alterations was performed according to the Boltzmann's equation as follows\(^{12}\),

\[
\hat{V}_{\text{max}} = \hat{V}_{\text{max}} \left(1 + \exp \frac{V - V_h}{s}\right)^{-1} \tag{6}
\]

where \( \hat{V}_{\text{max}} \) is \( \hat{V}_{\text{max}} \) obtained theoretically under the condition apparently free from the steady-state inactivation of \( I_{Na} \) (i.e., \([K^+]_e\) free condition) but assumed as \( \hat{V}_{\text{max}} \) under the minimum \([K^+]_e\) (i.e., 3.0 mM) in the present study. \( V \) and \( V_h \) are RMP providing respective \( \hat{V}_{\text{max}} \) and half-inactivation of \( \hat{V}_{\text{max}} \), and \( s \) is a slope factor.
Experimental protocols

After the preparation was subjected to half hour of equilibration, experimental protocol was commenced under the BCL of 1.0 sec. Aforementioned electrophysiologic parameters were evaluated under the different [K+]_e in the presence or absence of 100 μM nicorandil (n = 5 ~ 8). [K+]_e alteration was in the range of 3.0 to 12.0 mM, since further [K+]_e elevation induced the papillary muscle contracture and further [K+]_e reduction often evoked the abnormal automaticity of the preparation, both of which made the microelectrode impalement unstable. When data acquisition was disturbed by the poor microelectrode penetration, only the reliable data obtained under the stable impalement were analyzed. All experiments were conducted at the room temperature (22.3 ± 2.8 °C).

Data analysis and statistics

Data are presented as the mean ± SD. Comparison of various parameters among the different specific perfusion protocols was conducted by the paired t-test. Commercially available statistical software (Macintosh Expert Statview 4.0 system, Apple Japan, Tokyo, Japan) was used for practical analyses. Nonlinear regression analysis with least square method was conducted automatically by this computation. A p value less than 0.05 was considered statistically significant.

Results

As in Fig. 2,  \( V_{\text{max}} \) was plotted as a function of RMP under the [K+]_e alterations ranging from 3.0 to 12.0 mM. In the control condition, [K+]_e elevation shifted RMP to the positive direction and reduced  \( V_{\text{max}} \) dramatically, whereas [K+]_e reduction showed the opposite effects. This was the same when 100 μM nicorandil was introduced.  \( V_{\text{max}} \) in the minimum [K+]_e was significantly greater in the absence than in the presence of nicorandil (198.6 ± 8.6 vs. 191.3 ± 9.4 V/sec, p < 0.05). In the nonlinear fitting, these two conditions produced individually a significant (p < 0.05) correlation between RMP and  \( V_{\text{max}} \) (r = 0.853 and 0.903). The theoretical curve in the presence of nicorandil was superimposed completely by that in the control condition under the RMP less negative to −70 mV.  \( V_h \) and s were not fundamentally different between the two conditions (s: 3.59 vs. 3.44 mV,  \( V_h \): −63.2 vs. −62.5 mV).

In the control condition,  \( \theta \) showed complicated changes during the course of progressive [K+]_e elevation, i.e.,  \( \theta \) gradually increased as [K+]_e was elevated and was the maximum in the 9.0 mM [K+]_e, which was recognized as a supernormal conduction5110. Thereafter,  \( \theta \) was reduced dramatically by the further [K+]_e elevation up to 12.0 mM. On the other hand, [K+]_e reduction (3.0 mM) induced conduction slowing. The alterations of  \( \theta \) as a function of [K+]_e were investigated in the presence of 100 μM nicorandil. Biphasic changes of  \( \theta \) under the [K+]_e alterations (i.e., 3.0 to 12.0 mM) were observed, while supernormal conduction was noted in the 9.0 mM [K+]_e, as in the control condition (not shown). In the minimum [K+]_e of 3.0 mM,  \( V_i / V_e \) reflecting  \( r_i \) (equation [5]) was slightly increased from 13.1 to 14.9 by nicorandil.  \( \theta \) was slightly reduced (i.e., 58.8 to 56.5 cm/sec) and RMP shifted to the hyperpolarizing direction (i.e., −83.6 to −87.6 mV) by nicorandil (Fig. 3). By statistical analyses, conduction was slower (i.e., 57.0 ± 5.6 vs. 61.2 ± 6.1 cm/sec, p < 0.05) and RMP was more negative (−87.2 ± 2.0 vs. 191.3 ± 9.4 V/sec).
Various changes were observed by introducing nicorandil in the lowest $[K^+]_e$ (22.7 ± 2.3 vs. 21.3 ± 2.0 KΩ/cm, $p = 0.07$) and by minimizing $[K^+]_e$ in the presence of nicorandil (22.7 ± 2.3 vs. 21.8 ± 2.1 KΩ/cm, $p = 0.08$). Nicorandil and $[K^+]_e$ showed a great influence on the APD, in a complicated manner, irrespective of their dromotropic actions. APD showed a great $[K^+]_e$-dependence in the control condition, i.e., APD was lengthened as $[K^+]_e$ decreased and it was shortened as $[K^+]_e$ increased. Application of nicorandil generally shortened APD and this nicorandil-induced APD shortening was also $[K^+]_e$-dependent. This shortening was augmented as $[K^+]_e$ was lowered, i.e., it was significant ($p < 0.05$) in 3.0 and 5.4 mM $[K^+]_e$ but was not evident in 9.0 and 12.0 mM $[K^+]_e$ (Table).

Fig. 2 The alteration of the maximum rate of rise of the action potential upstroke ($V_{max}$) as a function of resting membrane potential (RMP) observed in the absence (open circles) or presence (closed circles) of 100 μM nicorandil. Nonlinear curve fitting was conducted by the Boltzmann's equation (equation [6] in the text). All symbols indicate mean ± SD. SD of RMP was too small to indicate outside of the symbols.

$-84.4 ± 1.8$ mV, $p < 0.05$) in the presence than in the absence of nicorandil.

The alterations of the three components of the longitudinal tissue resistance per unit length (i.e., $r_{total}$, $r_i$ and $r_e$) under the course of $[K^+]_e$ alterations were presented in Table. These components were stable during the $[K^+]_e$ alterations (3.0 to 12.0 mM) in the control aerobic condition. When nicorandil was applied, $r_{total}$ and $r_e$ were constant under the $[K^+]_e$ alterations and statistically the same as those in the control. With respect to $r_i$, no significant changes were observed by introducing nicorandil in the lowest $[K^+]_e$ (22.7 ± 2.3 vs. 21.3 ± 2.0 KΩ/cm, $p = 0.07$) and by minimizing $[K^+]_e$ in the presence of nicorandil (22.7 ± 2.3 vs. 21.8 ± 2.1 KΩ/cm, $p = 0.08$).

Nicorandil and $[K^+]_e$ showed a great influence on the APD, in a complicated manner, irrespective of their dromotropic actions. APD showed a great $[K^+]_e$-dependence in the control condition, i.e., APD was lengthened as $[K^+]_e$ decreased and it was shortened as $[K^+]_e$ increased. Application of nicorandil generally shortened APD and this nicorandil-induced APD shortening was also $[K^+]_e$-dependent. This shortening was augmented as $[K^+]_e$ was lowered, i.e., it was significant ($p < 0.05$) in 3.0 and 5.4 mM $[K^+]_e$ but was not evident in 9.0 and 12.0 mM $[K^+]_e$ (Table).

Discussion

Nicorandil exerts hybrid properties as a conventional nitrate compound and a $K_{ATP}$ channel opener and is recognized clinically as an antianginal and cardioprotective agent. Recently, this agent has been reported to be effective in specific kinds of arrhythmia which is not based on myocardial ischemia. Several basic investigations indicate that nicorandil exerts inhibitory actions on the afterdepolarization leading to the triggered arrhythmias in in vivo and in vitro models. This indicates that nicorandil-induced $K_{ATP}$ channel opening accelerates the action potential repolarization, normalizes the repolarization abnormalities and inhibits the triggered activities. Relatively to such antiarrhythmic actions of nicorandil, the dromotropic effects of this agent remain unclear. Therefore, this study was designed to investigate the
Dromotropic effects of nicorandil

Dromotropic actions of nicorandil under the \([K^+]_e\) alterations using guinea pig myocardium, since \([K^+]_e\) \textit{per se} also influences greatly the dromotropism and \(K^+\) channel activities. The present study showed great dependence on \([K^+]_e\) (ranging from 3.0 to 12.0 mM) of various electrophysiologic parameters relating to the action potential propagation and these parameters were modulated by nicorandil in a \([K^+]_e\)-dependent manner. Conduction speeding termed supernormal conduction\(^5\), in spite of a decrease in \(V_{\max}\), was observed under the slightly elevated (i.e., 9.0 mM) \([K^+]_e\) and marked conduction slowing was obtained by further \([K^+]_e\) elevation in this study. Nicorandil slowed conduction only in the minimum \([K^+]_e\) of 3.0 mM (Fig. 3) without changing fundamental relation between \(\theta\) and \([K^+]_e\) (Table). This is attributable to the nicorandil-induced small but significant fall in \(V_{\max}\) (Table) observed only in the lowest \([K^+]_e\). Low \([K^+]_e\) reduces theoretically the \(K^+\) conductance (\(g_k\)) of cardiac cell membrane, whereas nicorandil is expected to increase it as a \(K_{ATP}\) channel opener\(^1\), suggesting that electrophysiologic effects of nicorandil is manifest as \([K^+]_e\) decreases. \(V_{\max}\), as a simple measure of \(I_{Na}\) responsible for conduction, is greatest in a condition free from both \(I_{Na}\) inactivation and outward \(K^+\) current activation. In the present study, \(V_{\max}\) observed at the lowest \([K^+]_e\) was suppressed by nicorandil (Table). This implies that nicorandil increased the background \(g_k\) which shifted RMP to the hyperpolarized direction toward the \(K^+\) equilibrium potential (\(E_K\)), and augmented outward \(K^+\) current which may have partly antagonized \(I_{Na}\) without influencing \(I_{Na}\) inactivation kinetics (Fig. 2). No suppression of 100 \(\mu\)M nicorandil on \(V_{\max}\) in low (2.7 mM) \([K^+]_e\) was reported in the previous studies using canine Purkinje fibers\(^1\). This is due in part to the difference in preparations, i.e., \(V_{\max}\) in Purkinje fiber is far greater than that in myocardium.

Although nicorandil-induced cell-to-cell uncoupling was theoretically anticipated, no significant changes in \(r_1\) was observed by this agent (Table). Here, coupling coefficient (CC) is defined as a ratio of cellular gap junctional conductance (\(g_{gap}\)) divided by cellular membrane conductance (\(g_m\)) and is considered as one of the practical parameters responsible for cell-to-cell coupling, as follows\(^5\):

\[
CC = \frac{g_{gap}}{g_m} \quad [7]
\]

Nicorandil is expected to increase \(g_m\)
(~ gK at rest) as a K\textsubscript{ATP} channel opener\textsuperscript{(17,18)} and is known to increase cGMP levels in cardiovascular tissue\textsuperscript{(20)} due to the nitrate moiety in its molecule\textsuperscript{(8)}. Although the effects of cGMP on myocardial gap junction are complicated\textsuperscript{(21)}, Lucifer Yellow diffusion technique demonstrated no change in the diffusion coefficient in dog trabeculae\textsuperscript{(22)}, whereas patch clamp technique using neonatal rat heart cell pairs revealed fall in g\textsubscript{gap} \textsuperscript{(23)} by cGMP application. Based on equation \[7\], an increase in g\textsubscript{m} alone or in combination with a possible decrease in g\textsubscript{gap} leads theoretically to a decrease in CC, especially in the low [K\textsuperscript{+}]\textsubscript{e} condition. However, our study did not support this speculation probably due to an extent of the lowest [K\textsuperscript{+}]\textsubscript{e} in our experimental setting (i.e., 3.0 mM).

This study allows a few limitations. As a first one, the approximation of the steady state inactivation of I\textsubscript{Na} by the [K\textsuperscript{+}]\textsubscript{e}-dependent V\textsubscript{max} alteration is problematic. V\textsubscript{h} obtained by this study (i.e. −62 to −63 mV) shifted to the depolarized direction relative to V\textsubscript{h} of I\textsubscript{Na} (i.e. −72 to −94 mV) recorded in the single cardiomyocytes under the whole-cell patch clamp technique\textsuperscript{(24,25)}. Similarly, s in this study (about 3.5 mV) was exactly the same as in literature\textsuperscript{(20)} but quite smaller than that (ranging 5.1 to 6.9 mV) obtained by patch clamp study\textsuperscript{(24,25)}. These indicate that steady state inactivation of I\textsubscript{Na} is not negligible at RMP of about −90 mV, which value was obtained by the lowest [K\textsuperscript{+}]\textsubscript{e} in this study. Secondly, intrinsic problem of

<table>
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<th>Table</th>
<th>[K\textsuperscript{+}]\textsubscript{e}-dependent, nicorandil-induced alterations of electrophysiologic parameters</th>
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<tbody>
<tr>
<td>[K\textsuperscript{+}]\textsubscript{e} (mM)</td>
<td>3.0</td>
</tr>
<tr>
<td>(n)</td>
<td>(7)</td>
</tr>
<tr>
<td>V\textsubscript{max} (V/sec)</td>
<td>198.6 ± 8.6*</td>
</tr>
<tr>
<td>V\textsubscript{Na} (mV)</td>
<td>125.0 ± 5.1*</td>
</tr>
<tr>
<td>V\textsubscript{e} (mV)</td>
<td>9.4 ± 0.4*</td>
</tr>
<tr>
<td>r\textsubscript{total} (K\textomega/ cm)</td>
<td>1.74 ± 0.30</td>
</tr>
<tr>
<td>r\textsubscript{Na} (K\textomega/ cm)</td>
<td>1.75 ± 0.29</td>
</tr>
<tr>
<td>r\textsubscript{Na} (K\textomega/ cm)</td>
<td>1.87 ± 0.34</td>
</tr>
<tr>
<td>r\textsubscript{Na} (K\textomega/ cm)</td>
<td>1.88 ± 0.34</td>
</tr>
<tr>
<td>r\textsubscript{Na} (K\textomega/ cm)</td>
<td>21.3 ± 2.0</td>
</tr>
<tr>
<td>APD (msec)</td>
<td>232 ± 34**</td>
</tr>
<tr>
<td>(207 ± 36)**</td>
<td>171 ± 24*</td>
</tr>
</tbody>
</table>

Data are mean ± SD. APD, action potential duration at 90% repolarization; [K\textsuperscript{+}]\textsubscript{e}, external K\textsuperscript{+} concentration; r\textsubscript{Na}, r\textsubscript{Na}, r\textsubscript{Na}, external, internal and total longitudinal tissue resistance per unit length; \(\theta\), conduction velocity of excitation; V\textsubscript{e}, V\textsubscript{e}, extracellular and intracellular potential amplitudes, V\textsubscript{max}, the maximum rate of rise of the action potential upstroke. Upper and lower values in each parameter correspond to the absence and the presence of 100 µM nicorandil, respectively (n = 5~8). *p < 0.05 compared with respective control (i.e., drug-free) condition. *p < 0.05, and **p < 0.01 compared with 5.4 mM [K\textsuperscript{+}]\textsubscript{e} condition. Basic cycle length (BCL) of the stimulation was 1.0 sec throughout.
superfusion technique using tissue preparation should be noted. An extent of 100 μM nicorandil-induced APD shortening in 3.0 mM [K+]e in this study (~11 %) is quite less than that in the other studies using cardiomyocytes⁹ or tissue preparations¹⁷¹⁸ in the similar low (2.7 mM) [K+]e condition (17 % to 57 %). This may raise the problems of drug permeation and K⁺ or oxygen diffusion in the tissue preparation. Since APD is very sensitive to the local [K+]e or partial oxygen pressure and is influenced by electrotonic interactions¹⁰. However, nicorandil-induced, [K+]e-dependent APD shortening confirmed in this study is in accordance with previous study¹⁸. Cellular ATP content may vary depending on the preparations, leading to the variations of the effects of nicorandil on APD.

In conclusion, 100 μM nicorandil demonstrated [K+]e-dependent, mild but significant negative dromotropism. This phenomenon was accounted for by the cable analysis including cell-to-cell coupling concept and may contribute to the antiarrhythmic actions of nicorandil in the low [K+]e condition, which sometimes underlies the ischemia-related²⁷ or unrelated¹⁴¹⁵¹⁶ triggered arrhythmias.

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References


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モルモット乳頭筋における外液 K⁺濃度依存性の
ニコランジルの陰性変伝導作用

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