Hypertension

Laboratory Studies

Diltiazem and Left Ventricular Hypertrophy in Renovascular Hypertensive Rats

JEAN P. GRELLET, SIMONE M. BONORON-ADÉLE, LILIANE J. TARIOSSE, AND PIERRE J. BESSE

SUMMARY The effects of diltiazem treatment (40–50 mg/kg/day orally for 8 weeks) of left ventricular hypertrophy on systemic and coronary hemodynamics and mechanical cardiac performance were investigated in renovascular hypertensive rats (Goldblatt, two-kidney, one clip). Systemic and coronary hemodynamics were determined by using radioactive microspheres in conscious, unrestrained rats. Mechanical performance was measured on isolated papillary muscle from the same animal. Nine treated hypertensive rats were compared with control groups: 12 untreated hypertensive and nine sham-operated rats. Diltiazem treatment led to an effective but incomplete control of blood pressure (from 208 ± 5 mm Hg in the untreated hypertensive group to 155 ± 3 mm Hg in the treated hypertensive group; \( p < 0.01 \)) associated with a significant but incomplete decrease of the left ventricular mass (from 3.10 ± 0.19 mg/g in untreated hypertensive rats to 2.35 ± 0.04 mg/g in treated hypertensive rats; \( p < 0.01 \)). A close correlation was found between left ventricular mass and systolic blood pressure in untreated, treated, and pooled groups (\( r = 0.84, p < 0.001, n = 30 \)). The left ventricular weight to systolic blood pressure ratio was equivalent in all three groups, so that the reduction of left ventricular mass in diltiazem-treated rats was commensurate with the reduction of blood pressure. At rest, treated hypertensive rats showed a rise in cardiac output (426 ± 12 vs 298 ± 22 ml/min/kg in sham-operated rats; \( p < 0.001 \)) and in coronary blood flow (598 ± 17 vs 453 ± 19 ml/min/100 g; \( p < 0.05 \)) related to the decrease in total peripheral resistance and in total left ventricular coronary resistance. A reversal of impaired myocardial mechanical parameters toward control values was observed except for time to half-maximal relaxation (92 ± 2 msec in the treated group vs 79 ± 5 msec in sham-operated rats) and time to peak force. Our results demonstrate that even incomplete control of blood pressure with diltiazem is associated with significant but partial reduction of left ventricular mass and improvement of mechanical function.

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KEY WORDS • calcium antagonist • diltiazem • renovascular hypertension • left ventricular mass • myocardial perfusion • myocardial contraction

CALCIUM channel blocking agents are well known to have antihypertensive effects in humans, and in experimental hypertensive animal models. However, these drugs exhibit substantial differences in their antihypertensive potency, site of action, and degree of sympathetic stimulation. The 1,4-dihydropyridines are very potent antihypertensive drugs, with a proven ability to lower blood pressure and left ventricular mass. Less data are available about the effects of other antihypertensive calcium antagonist compounds on left ventricular hypertrophy. The present study was undertaken to evaluate the effects of diltiazem, a less vascular selective calcium entry blocker, on left ventricular hypertrophy, systemic and coronary hemodynamics, and isolated muscle mechanical performance in renovascular hypertensive rats (RHR; two-kidney, one clip, Goldblatt model).

Materials and Methods

Preparation of Renal Hypertensive and Sham-Operated Rats

Thirty male Sprague-Dawley rats, aged 40 to 50 days with weights ranging between 150 and 180 g, were purchased from Janvier Laboratory (Genest-
Saint-Berthevin, France). Two-kidney, one clip hypertension (Goldblatt model) was induced in 21 of them (RHR) by placing a silver clip (aperture, 0.25 mm) on the left artery while the rats were under ether anesthesia. The contralateral kidney was left untouched. Nine rats had a similar operation without vascular clipping (sham operation) and were used as controls (SHC). Systolic blood pressure (SBP) was measured by the tail-cuff method before operation and at 1-week intervals thereafter. Rats were considered hypertensive when SBP reached 160 mm Hg, which generally occurred within 2 weeks of clipping. RHR and SHC were housed at constant temperature in environmental facilities and were given standard laboratory chow and water ad libitum.

Treatment of Hypertension

Eight weeks after clipping, the RHR were divided randomly into two groups: The first group (n = 12) was left untreated (RHR-U), and the second group (n = 9) was treated with diltiazem (LERS Laboratory, Synthelabo, Paris, France; RHR-T). Evolution of blood pressure was carefully monitored each day during the first week of treatment. The criterion used to establish dosage was effective blood pressure control. RHR-T were given diltiazem in drinking water at an initial dose of 30 mg/kg/day. The dosage was gradually increased to 40–50 mg/kg/day and adjusted for each animal to maintain blood pressure levels near 150 mm Hg. Rats were then given the adjusted dose during 8 weeks of treatment before the final hemodynamic and mechanical measurements were performed. During this period, blood pressure was measured twice a week by the same person at the same time of day.

Systemic and Coronary Blood Flow Determination

Cardiac output and coronary blood flow were measured at rest and after coronary dilatation by carbocromen in conscious, unrestrained rats by using left atrial injection of radioactive microspheres as described in detail by Wicker and Tarazi.13,14 Briefly, a No. 1 polyethylene catheter (Biotrol Pharma, Paris, France) was placed into the left atrium and exteriorized on the back of the neck while the rats were under pentobarbital anesthesia (30 mg/kg i.p.). Twelve hours before the study, another catheter (Biotrol No. 3) was inserted through a femoral artery into the abdominal aorta. Just before experimentation, this catheter was connected to a pressure transducer and an infusion withdrawal pump (Harvard Apparatus, Natick, MA, USA). This system allowed us to record blood pressures just before and after hemodynamic measurements and to withdraw reference blood samples for determination of cardiac output. Before injection, radioactive microspheres (15 μm in diameter) labeled with either cerium-141 or strontium-85 (3M Company, Saint Paul, MN, USA) were prepared as previously described.13–16

A total of 0.15 ml of microsphere suspension was withdrawn in a Biotrol No. 3 catheter corresponding to 300,000 spheres and counted for radioactivity determination. The microspheres were injected into the left atrium over a period of 10 seconds, and the catheter was rapidly flushed with 0.2 ml of saline. Starting 10 seconds before the injection, a blood sample was withdrawn for 70 seconds through the femoral catheter at a constant rate of 0.425 ml/min. The rat was then given 0.2 ml of saline so that blood mass remained unchanged after hemodynamic determinations.

After the baseline measurement, coronary vasodilatation was induced by carbocromen, 9 mg/kg, infused at a constant rate of 0.17 ml/min through the left atrial catheter. Five minutes after the end of the carbocromen infusion, hemodynamic measurements were repeated with a second batch of differently labeled radioisotope microspheres.

After hemodynamic data were collected, the animals were killed with an air bolus and their hearts removed immediately. This killing method also allowed mechanical performance to be measured on isolated papillary muscle.12 After rapid removal of the papillary muscle from left ventricle, right ventricle, endocardium, epicardium, and septum were dissected away, prepared for gamma counting, and weighed with precision. Tissue and blood samples were placed in separate plastic tubes and counted in a gamma counter (LKB Wallac Clinigamma, Paris, France).

Mechanical Cardiac Performance Measurements

Muscles removed from left ventricles were suspended at 29°C in an organ bath (50 ml) containing 50 ml of a modified, normotonic Krebs-Ringer solution (290 mosm): 118 mM NaCl, 4.7 mM KCl, 1.1 mM MgSO4·7H2O, 1.1 mM KH2PO4, 24 mM NaHCO3, 2.5 mM CaCl2·2H2O, and 4.5 mM glucose, buffered at pH 7.4. A gas mixture of 95% O2 and 5% CO2 was bubbled through this solution (oxygen tension, 630 mm Hg). The muscles were electrically stimulated (Roucaille T stimulator, Velizy, France) at a frequency of 6/min, with rectangular pulses of 5 msec. The voltage of these pulses exceeded the stimulation threshold by about 10%. The stimulus was provided through two parallel platinum electrodes. Perfect stabilization was obtained after at least 3 to 4 hours of isotonic beating against a moderate afterload (1–3 g according to initial developed tension). The muscle was then "stretched" to the peak of its length active force curve (i.e., Lmax).

An electromagnetic lever similar to that previously described by Brutsaert and Claes19 but with a smaller moving mass (155 mg) allowed the automatic adjustment of the preload constraint and the imposition of different loads during the contractions.18,19 The force transducer (manufactured by Dr. Claes, University of Antwerp, Antwerpen, Belgium) was similar to the
type described by Goethals et al., with a reduced total compliance of 3 μg/g of load. A computer was used to command the apparatus and to obtain the results.

The mechanical performance was determined from consecutive contractions following a series of stable isotonic contractions at L_{max}. Subsequently, the following variables were measured: the shortening amplitude, peak contraction velocity at L_{max} preload, and peak relaxation velocity during an isotonic contraction, and the peak total tension, time to peak total tension (TPF), and time to half-maximal relaxation (THR) during an isometric contraction.

Quantification of the effects of loading on load dependence of relaxation was done according to the method proposed by Chuck et al., with the ratio of load-sensitive; if this ratio was equal to 1.0, relaxation was termed load insensitive.

Data Calculation and Statistical Analysis

Cardiac output and coronary blood flow were computed from radioactivity in tissues and blood samples according to standard formulas. Left ventricular coronary vascular resistance was calculated by dividing the mean aortic pressure by the left ventricular coronary flow. Left ventricular coronary flow and resistance were normalized to 100 g of left ventricular weight.

Values reported represent the means ± SE. Analysis of variance was used for multiple group comparisons. When significant p values were obtained, all pairs of means were compared with a Newman-Keuls multiple range test. Statistical significance was determined as a p level below 0.05. Relations between left ventricular mass normalized for body weight (LVW) and SBP were tested by linear regression analysis.

Results

Blood Pressure Control and Reversal of Left Ventricular Hypertrophy Through Diltiazem Therapy

SBP, measured by the tail-cuff method, was markedly increased in RHR-U 8 weeks after clipping (208 ± 7 vs 137 ± 6 mm Hg in SHC; p < 0.01). Oral administration of diltiazem (40–50 mg/kg/day) to RHR resulted in a significant decrease of SBP (p < 0.01; Table 1). This hypotensive response was seen after 1 week and continued throughout the treatment period.

Mean arterial pressure (MAP) measured with the femoral artery catheter just before the injection of microspheres is summarized in Table 1. Values in RHR-U and RHR-T were significantly different from those in SHC (p < 0.01). Diltiazem treatment reduced MAP in RHR-T, but the pressure level remained higher in RHR-T than in SHC (p < 0.01).

LVW was significantly greater in RHR-T and RHR-U than in SHC (p < 0.01; see Table 1). Oral administration of diltiazem significantly reduced LVW in RHR-T, but values in RHR-U remained significantly higher than those in SHC (p < 0.01).

A significantly positive correlation was observed between LVW and SBP in SHC, RHR-U, and RHR-T (r = 0.84, p < 0.001, n = 30, Figure 1). A close correlation was also found between LVW and SBP in RHR-T and RHR-U. The slopes of the regression lines were not statistically different from each other so that the LVW/SBP ratio was equivalent in RHR-T and RHR-U.

Systemic and Coronary Hemodynamics

Cardiac output did not differ between SHC and RHR-U, but it was elevated significantly in RHR-T compared with SHC (p < 0.01; see Table 1). The high blood pressure level in RHR-U was supported by a significant increase in total peripheral resistance compared with SHC (p < 0.01; see Table 1). Diltiazem therapy resulted in an important decrease of total peripheral resistance. Its average value was significantly smaller in RHR-T than in RHR-U (p < 0.01) and in SHC (p < 0.05).

There were no significant differences in heart rate among the three experimental groups.

Left ventricular coronary blood flow per unit mass did not differ at rest among SHC and RHR-U (Table 2). Diltiazem administration resulted in a significant

Table 1. Systemic Hemodynamic Effects of 8 Weeks of Diltiazem Treatment (40-50 mg/kg/day p.o.) in Renovascular Hypertensive Rats

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sham-operated rats (n = 9)</th>
<th>Untreated (n = 12)</th>
<th>Treated (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>388 ± 17</td>
<td>345 ± 20</td>
<td>345 ± 6</td>
</tr>
<tr>
<td>LVW (mg/g)</td>
<td>2 ± 0.09</td>
<td>3.10 ± 0.19*</td>
<td>2.35 ± 0.04*†</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>416 ± 14</td>
<td>426 ± 17</td>
<td>404 ± 5</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>137 ± 6</td>
<td>208 ± 5*</td>
<td>155 ± 3*†</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>106 ± 6</td>
<td>156 ± 7*</td>
<td>125 ± 3*†</td>
</tr>
<tr>
<td>CO (ml/min/kg)</td>
<td>298 ± 22</td>
<td>314 ± 16</td>
<td>426 ± 12*†</td>
</tr>
<tr>
<td>TPR (mm Hg·min⁻¹·kg⁻¹)</td>
<td>0.363 ± 0.025</td>
<td>0.489 ± 0.024*</td>
<td>0.295 ± 0.008†</td>
</tr>
</tbody>
</table>

Values are means ± SE. LVW = left ventricular mass normalized for body weight; HR = heart rate; CO = cardiac output; TPR = total peripheral resistance.

*p < 0.01, †p < 0.05, compared with values for sham-operated controls.

*p < 0.01, compared with values for untreated hypertensive rats.
increase of left ventricular coronary flow at rest in RHR-T compared with SHC \((p < 0.01)\) that was associated with a significant reduction in total coronary vascular resistance \((p < 0.05)\). Following carbocromen infusion, coronary flow significantly increased in all rats. The maximal left ventricular coronary flows and the minimal coronary vascular resistances were not significantly different in SHC, RHR-U, and RHR-T (see Table 2).

Coronary flow reserve, in terms of capacity to increase flow in response to a coronary vasodilator stimulus, was not modified in RHR-T and RHR-U (see Table 2). However, when expressed as percent change from resting values, coronary flow reserve was lower in RHR-T than in the other two groups \((p < 0.05)\). In addition, coronary vasodilator reserve, computed either in absolute units (mm Hg/ml/min) or as percent change from resting values, was significantly lower in RHR-T than in RHR-U and SHC \((p < 0.05)\).

The distribution of coronary blood flow between endocardium and epicardium was measured by means of the endocardial/epicardial flow ratio. At rest, this ratio approximated unity in all groups (see Table 2). Carbocromen vasodilation resulted in a reduction of the endocardial/epicardial flow ratio. The intergroup differences for this parameter were not significant at rest and after carbocromen infusion.

**Table 2.** Coronary Hemodynamic Effects of 8 Weeks of Diltiazem Treatment (40–50 mg/kg/day) in Renovascular Hypertensive Rats

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sham-operated rats ((n = 9))</th>
<th>Untreated rats ((n = 12))</th>
<th>Treated rats ((n = 9))</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVCF (ml/min/100 g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At rest</td>
<td>453 ± 19</td>
<td>549 ± 48</td>
<td>598 ± 17*</td>
</tr>
<tr>
<td>After carbocromen infusion, maximal flow</td>
<td>1521 ± 153</td>
<td>1618 ± 77</td>
<td>1474 ± 79</td>
</tr>
<tr>
<td>Coronary flow reserve (ml/min/100 g)</td>
<td>1102 ± 168</td>
<td>1068 ± 109</td>
<td>909 ± 79</td>
</tr>
<tr>
<td>Percent increase</td>
<td>242 ± 41</td>
<td>209 ± 38</td>
<td>151 ± 7†</td>
</tr>
<tr>
<td>TCVR (mm Hg/ml/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At rest</td>
<td>31.5 ± 3</td>
<td>29.7 ± 3.5</td>
<td>26.0 ± 0.8†</td>
</tr>
<tr>
<td>After carbocromen infusion, minimal TCVR</td>
<td>8.38 ± 0.53</td>
<td>8.56 ± 0.60</td>
<td>9.69 ± 0.53</td>
</tr>
<tr>
<td>Coronary vasodilator reserve (mm Hg/ml/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At rest</td>
<td>-23.1 ± 2.9</td>
<td>-21.1 ± 3.3</td>
<td>-16.3 ± 0.80†</td>
</tr>
<tr>
<td>Percent change</td>
<td>-73.3 ± 3.0</td>
<td>-71.0 ± 3.3</td>
<td>-62.7 ± 2.2†‡</td>
</tr>
<tr>
<td>Endocardial/epicardial flow</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At rest</td>
<td>1.015 ± 0.050</td>
<td>1.040 ± 0.031</td>
<td>1.041 ± 0.032</td>
</tr>
<tr>
<td>After carbocromen infusion</td>
<td>0.823 ± 0.037</td>
<td>0.852 ± 0.039</td>
<td>0.849 ± 0.032</td>
</tr>
</tbody>
</table>

Values are means ± SE. LVCF = left ventricular coronary flow; TCVR = total coronary vascular resistance.

*\(p < 0.01\), †\(p < 0.05\), compared with values for sham-operated controls.

‡\(p < 0.05\), compared with values for untreated hypertensive rats.
of adrenergic response. In our study, the regression lines were very close in treated and untreated groups. This superimposition suggests that the incomplete regression of LVW may be related to the incomplete control of blood pressure alone. It is not surprising since the adrenergic response to diltiazem was less important as compared with those to nitrendipine and nifedipine.6 Moreover, this result is inconsistent with a direct effect of diltiazem on left ventricular hypertrophy, as speculated by Tubau et al.33

Systemic Hemodynamic Data
Cardiac output did not differ between untreated groups. The rise in blood pressure was related to a proportional increase in total peripheral resistance. Diltiazem treatment led to an increase in cardiac output without any change in heart rate. Since diltiazem itself had a negative inotropic effect on isolated heart muscle,6 the increased stroke volume cannot be related to a direct effect of this drug on myocardial tissue. Therefore, it is reasonable to assume that the rise in cardiac output was due to the ability of diltiazem to reduce the total peripheral vascular resistance.

Coronary Hemodynamics
Left ventricular coronary flow, expressed per 100 g of myocardial tissue, and total coronary resistance remained unchanged in hypertensive rats under both resting and maximal vasodilating conditions. Except for unchanged coronary flow reserve, these results are in agreement with most of the reported data.9, 15, 37 The maintenance of total coronary resistance suggests that the functional cross-sectional area of the coronary circulation does not grow in parallel with ventricular mass.38 In accordance with Wicker and Tarazi,37 the level of maximal coronary blood flow was closely correlated with the value of the MAP/LVW ratio. In our experiment, maintenance of this ratio could explain the unchanged maximal coronary blood flow.

Under resting conditions, diltiazem produced a significant increase in left ventricular coronary flow. The observed rise in cardiac output was not high enough in terms of myocardial oxygen consumption to explain this change in coronary blood flow. Diltiazem's elimination half-life is short in rats (approximately 1 hour).39 In this context, low levels of diltiazem were conceivable at the time of the hemodynamic measurements; however, increased stroke volume and coronary blood flow cannot be related to an acute effect of this drug. Under similar conditions, at the time of hemodynamic measurements, diltiazem treatment resulted in an increased coronary blood flow and stroke volume in normal rats (unpublished results, 1987). These data suggest a residual systemic and coronary vasodilating action of diltiazem at the times of the hemodynamic measurements. Hemodynamic data did not allow conclusions with reference to any diltiazem-induced beneficial change in coronary circulation in RHR associated with reversal of the early phase of left ventricular hypertrophy since 1) coronary hemodynam-

**Table 3. Effect of 8 Weeks of Diltiazem Treatment (40-50 mg/kg/day) on Mechanical Performance in Renovascular Hypertensive Rats**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sham-operated rats (n = 19)</th>
<th>Untreated rats (n = 12)</th>
<th>Treated rats (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF (g/mm²)</td>
<td>2.49 ± 0.35</td>
<td>4.03 ± 0.31*</td>
<td>3.05 ± 0.17</td>
</tr>
<tr>
<td>dL (mm)</td>
<td>0.125 ± 0.016</td>
<td>0.114 ± 0.08</td>
<td>0.122 ± 0.013</td>
</tr>
<tr>
<td>dL/dt (sec⁻¹)</td>
<td>1.89 ± 0.12</td>
<td>1.3 ± 0.10*</td>
<td>1.69 ± 0.06</td>
</tr>
<tr>
<td>V_max (sec⁻¹)</td>
<td>2.15 ± 0.31</td>
<td>1.88 ± 0.20*</td>
<td>2.51 ± 0.22</td>
</tr>
<tr>
<td>TPF (msec)</td>
<td>104 ± 3</td>
<td>130 ± 6*</td>
<td>119 ± 4*†</td>
</tr>
<tr>
<td>THR (msec)</td>
<td>79 ± 5</td>
<td>100 ± 6†</td>
<td>92 ± 2†</td>
</tr>
<tr>
<td>dR/L (sec⁻¹)</td>
<td>0.875 ± 0.011</td>
<td>0.885 ± 0.012</td>
<td>0.860 ± 0.025</td>
</tr>
</tbody>
</table>

Values are means ± SE. PF = developed isometric tension; dL = shortening amplitude; dL/dt = peak velocity of shortening; V_max = peak relaxation velocity; TPF = time to peak force; THR = time to half-maximal relaxation; dR/L = time to relaxation index.

* p < 0.01, † p < 0.05, compared with values for sham-operated controls.

‡ p < 0.05, compared with values for untreated hypertensive rats.

**Discussion**
In the present study, orally administered diltiazem doses were adjusted for each animal and resulted in a 18 to 30% decrease of pressure in nine of 12 RHR-T. In accordance with previous studies,27, 28 the method of drug administration, using 40 to 50 mg/kg/day, ensured a continuous lowering of blood pressure throughout the day. The lack of efficacy in three rats was correlated to very high levels of blood pressure (SBP > 220 mm Hg), so that diltiazem seemed to be unable to control severe hypertension despite the administration of large amounts (>70 mg/kg/day). These three animals were consequently excluded from the experimental RHR-T group. Diltiazem maintained its ability to lower blood pressure throughout the 8 weeks of treatment without any rise during the final weeks. The hypotensive response was still effective at the time of the hemodynamic measurements, 12 hours after the last administration of the drug. The decrease of blood pressure in RHR-T was associated with a significant but incomplete reduction in LVW. A close linear relation was found between LVW and SBP in both untreated groups. The rise in blood pressure was related to a proportional increase in total peripheral resistance.

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...
ics remained unchanged in RHR-U and 2) comparable results were obtained in SHC.

Mechanical Performance
Previous studies in both humans and animals have evidenced an impairment of contractility and relaxation in ventricular hypertrophy. Mechanical performance changes in animal models vary according to the stimulus used to induce hypertrophy, the duration of pressure load, and the animal species. In rats with hypertrophy induced by pressure load, most studies report increased isometric timing parameters (TPF and THR), decreased velocity of shortening and velocity of relaxation, and normal or increased peak tension values. Our experimental data are in agreement with these previous results. In rats, reduced velocity of shortening can be correlated with the decrease in myosin adenosine triphosphatase activity due to an isoenzymatic pattern change. The longer duration of isometric contraction (increase in THR and TPF) may be related to the increased action potential duration observed in hypertrophied muscles.

Delayed relaxation of myocardial fiber (decrease in peak relaxation velocity) cannot be attributed to an alteration of the sarcoplasmic reticulum function, since load dependence of relaxation was not altered. Diltiazem treatment led to a normalization of mechanical parameters except for THR and TPF. The lack of total reversal of isometric timing parameters could be related to the incomplete left ventricular mass regression. However, a similar result was obtained after 8 weeks of treatment with a new converting enzyme inhibitor despite total regression of left ventricular mass. Therefore, an additional factor seems to be involved in the maintenance of a delayed isometric contraction. A possible explanation may be the maintenance of a longer action potential duration.

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