Aldose reductase inhibition alone or combined with an adenosine A3 agonist reduces ischemic myocardial injury

W. ROSS TRACEY, WILLIAM P. MAGEE, CRAIG A. ELLERY, JOSEPH T. MACANDREW, ANDREW H. SMITH, DELVIN R. KNIGHT, AND PETER J. OATES

Department of Cardiovascular and Metabolic Diseases,
Pfizer, Incorporated, Groton, Connecticut 06340

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Tracey, W. Ross, William P. Magee, Craig A. Ellery, Joseph T. MacAndrew, Andrew H. Smith, Delvin R. Knight, and Peter J. Oates. Aldose reductase inhibition alone or combined with an adenosine A3 agonist reduces ischemic myocardial injury. Am J Physiol Heart Circ Physiol 279: H1447–H1452, 2000.—This study investigated whether aldose reductase (AR) inhibition with zopolrestat, either alone or in combination with an adenosine A3-receptor agonist (CB-MECA), reduced myocardial ischemic injury in rabbit hearts subjected to 30 min of regional ischemia and 120 min of reperfusion. Zopolrestat reduced infarct size by up to 61%, both in vitro (2 nM to 1 μM; EC50 = 24 nM) and in vivo (50 mg/kg). Zopolrestat reduced myocardial sorbitol concentration (index of AR activity) by >50% (control, 15.0 ± 2.2 nmol/g; 200 nM zopolrestat, 6.7 ± 1.3 nmol/g). A modestly cardioprotective concentration of CB-MECA (0.2 nM) allowed a 50-fold reduction in zopolrestat concentration while providing a similar reduction in infarct size (infarct area/area at risk: control, 62 ± 2%; 1 μM zopolrestat, 24 ± 5%; 20 nM zopolrestat plus 0.2 nM CB-MECA, 20 ± 4%). In conclusion, AR inhibition is cardioprotective both in vitro and in vivo. Furthermore, combining zopolrestat with an A3 agonist allows a reduction in the zopolrestat concentration while maintaining an equivalent degree of cardioprotection.

Methods

Ischemic preconditioning (12), a phenomenon in which a brief ischemic event protects the myocardium from a subsequent prolonged ischemic insult, is thought to involve several paracrine or autocrine factors that act directly or indirectly on transmembrane receptors or ion channels (reviewed in Refs. 15, 19, 28). Metabolic consequences associated with ischemic preconditioning include glycogen depletion (4, 11, 20, 27), preservation of ATP and creatine phosphate content during ischemia (4, 7, 8, 13, 20, 25), inhibition of glycolysis (4, 13), and reduced lactate accumulation (7, 13, 25). Recently, a role for the polyol (sorbitol) pathway in myocardial ischemia-reperfusion injury was implicated by the observation that the aldose reductase inhibitor (ARI) zopolrestat (3,4-dihydro-4-oxo-3-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]-1-phthalazineacetic acid) (14) improved functional recovery and slowed the loss of high-energy phosphates in diabetic rat hearts subjected to ischemia-reperfusion injury (17, 18). Whether cardioprotection with zopolrestat is species-specific or whether aldose reductase inhibition can reduce infarct size in a manner similar to that observed with ischemic preconditioning is unknown. Therefore, we investigated whether zopolrestat would reduce infarct size, in vitro and in vivo, in nondiabetic rabbit models of myocardial ischemia-reperfusion injury and compared the ARI-dependent cardioprotection to ischemic preconditioning. Furthermore, because we have previously demonstrated that selective stimulation of adenosine A3 receptors can pharmacologically precondition rabbit myocardium (5, 22, 23), we examined whether a combination of zopolrestat and an A3-receptor agonist would provide additional reductions in myocardial ischemic injury in vitro.

 METHODS

This investigation conforms to the Guide for the Care and Use of Laboratory Animals published by the Institute of Laboratory Animal Resources (NRC, 1996).

In vitro (Langendorff) preparation. Male New Zealand white rabbits (3–4 kg; Covance, Denver, PA) were anesthetized by administration of pentobarbital sodium (30 mg/kg iv), followed by intubation and ventilation with 100% O2 using a positive-pressure ventilator. A left thoracotomy was performed, the heart was exposed, and a snare (2–0 silk) was placed loosely around a prominent branch of the left coronary artery. The heart was rapidly removed from the chest, mounted on a Langendorff apparatus, and maintained by retrograde perfusion (nonrecirculating) with a modified Krebs solution (in mM: 118.5 NaCl, 4.7 KCl, 1.2 MgSO4, 1.2 KH2PO4, 24.8 NaHCO3, 2.5 CaCl2, and 10 glucose) at a constant pressure of 80 mmHg and a temperature of 38.5°C. Perfusate pH was maintained at 7.4–7.5 by bubbling with 95% O2-5% CO2. The temperature of the heart was maintained by suspending it in a heated, water-jacketed organ bath. A fluid-filled latex balloon was inserted in the left ventricle and connected by stainless steel tubing to a pressure transducer; the balloon was inflated to provide a systolic pressure of 80–120 mmHg and a diastolic pressure ≤10 mm Hg.
mmHg. Heart rate (HR), left ventricular diastolic and systolic pressures, and left ventricular developed pressure (LVDP) were recorded using a PO-NE-MAH Data Acquisition and Archive System (Gould Instrument Systems, Valley View, OH). Coronary flow rate (CF) was determined using an in-line flow probe (Transonic Systems, Ithaca, NY); coronary flow was normalized for heart weight. Each heart was allowed to equilibrate for 30 min, and if stable left ventricular pressures within the parameters outlined above were not observed, the heart was discarded. Pacing was not used unless the heart rate fell below 180 beats/min before the 30-min period of regional ischemia; in this case, the heart was paced at 200 beats/min, which was the average spontaneous rate observed.

**Langendorff experimental protocols.** Zopolrestat (an aldose reductase inhibitor), CB-MECA \([N^6-(3-chlorobenzyl)-5'-N-methylcarboxamido]adenosine, an adenosine A3-receptor agonist\], or a combination of the two drugs were perfused through the heart for 5 min, followed by a 10-min washout (Fig. 1). For comparative purposes, some hearts were preconditioned by 5 min of global ischemia and 10 min of reperfusion. Thirty minutes of regional ischemia was then produced by tightening the snare around the branch of the coronary artery. At the end of this period, the snare was released and the heart was reperfused for an additional 120 min.

**In vivo preparation.** Twenty-six fed New Zealand White male rabbits (3–4 kg) were anesthetized with pentobarbital sodium (30 mg/kg iv), and a surgical plane of anesthesia was maintained by a continuous infusion of pentobarbital sodium (12 mg·kg⁻¹·h⁻¹) via an ear vein catheter. A tracheotomy was performed through a ventral midline cervical incision, and the rabbits were ventilated with 100% oxygen using a positive-pressure ventilator. Body temperature was maintained at 38.5°C using a heating pad connected to a temperature controller (model 72, Yellow Springs Instruments, Yellow Springs, MD). Fluid-filled catheters were placed in the left jugular vein for drug administration and in the left carotid artery for blood gas analysis using a blood gas analyzer (model 248, Chiron Diagnostic, Norwood, MA) and for blood pressure measurements. The ventilator was adjusted as needed to maintain blood pH and Pco₂ within normal physiological ranges for rabbits. The heart was exposed through a left thoracotomy at the fourth intercostal space and a 2–0 silk suture was placed around a prominent branch of the left coronary artery. Lead II ECG was measured using an electrocardiogram (ECG) amplifier (Gould, Cleveland, OH) connected to surface ECG electrodes. Arterial pressure was measured using a calibrated strain-gauge transducer (Spectromed, Oxnard, CA) connected to the arterial catheter. HR and mean arterial pressure (MAP) were derived using the PO-NE-MAH system. Rate-pressure product (RPP) was calculated as the product of HR and MAP. RPP has been previously used as an index of myocardial O₂ consumption in this model (9).

**In vivo experimental protocols.** Ninety minutes after surgery, when arterial pressure, HR, and RPP had stabilized for

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**Fig. 1. Experimental protocols.**

Ischemic Preconditioning

- Equilibration (30 min)
- Regional ischemia (30 min)
- Reperfusion (120 min)
- Measure infarct size

In vitro:

- Zopolrestat/CB-MECA Administration
  - Equilibration (30 min)
  - Regional ischemia (30 min)
  - Reperfusion (120 min)
  - Measure infarct size

In vivo:

- Baseline (30 min)
- Regional ischemia (30 min)
- Reperfusion (120 min)
- Measure infarct size

Zopolrestat infusion (30 min)
at least 30 min (baseline), the experiment was started following the protocols shown in Fig. 1. Zopolrestat (50 mg/kg) was infused for 30 min or, for comparative purposes, some hearts were preconditioned by 5 min of regional ischemia and 10 min of reperfusion. Regional ischemia was produced by tightening the coronary artery snare for 30 min. The snare was released, and the heart was reperfused for an additional 120 min. Myocardial ischemia was evidenced by regional cyanosis and S-T segment elevation; reperfusion was evidenced by reactive hyperemia and rapid decline of the S-T segment elevation. At the end of reperfusion, each rabbit was euthanized with an overdose of pentobarbital sodium (100 mg/kg iv). The heart was quickly excised, mounted on a Langendorff apparatus, and perfused with physiological saline at 38.5°C.

**Determination of infarct size.** After completion of each experiment and with the heart suspended and perfused on the Langendorff apparatus, the coronary artery snare was retightened and a 0.5% suspension of fluorescent zinc cadmium sulfate particles (1–10 μm) was perfused through the heart to delineate the area at risk (nonlabeled) for infarct development. The heart was removed from the Langendorff apparatus, blotted dry, weighed, wrapped in aluminum foil, and stored overnight at −20°C. Frozen hearts were sliced into 2-mm transverse sections and incubated with 1% triphenyl tetrazolium chloride in phosphate-buffered saline for 20 min at 37°C to delineate noninfarcted (stained) from infarcted (nonstained) tissue. The infarct area and the area at risk were calculated for each slice of left ventricle using a calibrated image analyzer (Optomax V Image Analyzer, AMS, Burlington, MA), and then the values for each tissue slice were added to obtain the total infarct area and total area at risk for each heart. To normalize the infarct area for differences in the area at risk between hearts, the infarct size was expressed as the ratio of infarct area versus the area at risk (%IA/AAR).

**Determination of myocardial sorbitol concentrations.** Zopolrestat or zopolrestat plus CB-MECA was perfused through isolated hearts for 5 min followed by a 10-min washout. Each heart was then removed from the Langendorff apparatus (i.e., just before the 30-min ischemic period). The atria were quickly removed, and the ventricles were snap-frozen in liquid nitrogen. Approximately 500 mg of frozen ventricle was placed in a 16 × 100-mm glass test tube to which 3.0 ml of water (milli-Q plus, Millipore) was added. This was followed by heating the tube to 100°C for 15 min in a heating block. The tissue in each tube was then homogenized, and protein precipitated by addition of 3.0 ml of 0.3 M ZnSO₄ followed by 3.0 ml of 0.3 M Ba(OH)₂. After the tubes stood on ice for 30 min, tubes were centrifuged at 2,700 g for 20 min at 4°C. A 0.04-ml aliquot of supernatant fluid was analyzed for sorbitol using a modification of the enzymatic method described by Malone et al. (10). Final reagent concentrations were 0.2 M triethanolamine buffer (pH 8.5), 1.2 μM resazurin (Aldrich Chemical), 1 mM NAD⁺, and 0.3 U/ml diaphorase (Sigma Chemical), with or without 15 U/ml sorbitol dehydrogenase (Boehringer Mannheim). Samples were incubated at room temperature (22°C) for 60 min. Fluorescence intensity (model LS-50B, Perkin-Elmer, Norwalk, CT) was measured at an emission wavelength of 580 nm, with an excitation wavelength of 560 nm and slit widths of 10 nm.

**Data expression and analysis.** Data are expressed as means ± SE. Between-group comparisons of baseline in vivo hemodynamic variables, in vitro areas at risk, and in vivo areas at risk were compared using ANOVA. Comparisons of in vivo hemodynamic parameters between zopolrestat and vehicle control over the course of the study were performed using ANOVA with repeated measures. Both in vitro hemodynamic variable comparisons and sorbitol concentration comparisons were performed by Student’s t-test, whereas in vitro %IA/AAR values and in vivo %IA/AAR values were compared using a Mann-Whitney test and aBonferroni correction was applied to multiple comparisons. To determine whether the combination of zopolrestat and CB-MECA produced an additive versus a synergistic increase in cardioprotection relative to either agent alone, the infarct area (%IA/AAR) were analyzed using two-way ANOVA with interaction. P < 0.05 was considered statistically significant.

**Drugs and drug preparation.** Zopolrestat and CB-MECA were synthesized at Pfizer Central Research (Groton, CT). All drugs administered to the isolated hearts were dissolved in DMSO and diluted in buffer; the final DMSO concentration was <0.1%, which had no effect on infarct size (22). For the in vivo studies, zopolrestat was dissolved in normal saline, pH 8.0, at a concentration of 8 mg/ml and delivered at a dose volume of 6.25 ml/kg over 30 min. This dose represents the highest concentration of zopolrestat that remained in solution without adding solubilizing agents and constitutes the highest dose volume over 30 min that did not cause hemodynamic effects in rabbits.

**RESULTS**

Baseline HR, CF, and LVDP values for each of the Langendorff treatment groups were similar before the regional ischemia was performed and are shown in Table 1. Hemodynamic data from isolated rabbit hearts

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Preocclusion HR (beats/min)</th>
<th>Preocclusion CF (ml·min⁻¹·g⁻¹)</th>
<th>Preocclusion LVDP (mmHg)</th>
<th>Post-30-Min Occlusion HR (beats/min)</th>
<th>Post-30-Min Occlusion CF (ml·min⁻¹·g⁻¹)</th>
<th>Post-30-Min Occlusion LVDP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>6</td>
<td>202 ± 8</td>
<td>7.0 ± 0.6</td>
<td>108 ± 3</td>
<td>197 ± 5</td>
<td>5.1 ± 0.3*</td>
<td>72 ± 5*</td>
</tr>
<tr>
<td>Ischemic preconditioning</td>
<td>5</td>
<td>208 ± 6</td>
<td>7.0 ± 0.4</td>
<td>95 ± 4</td>
<td>213 ± 6</td>
<td>5.5 ± 0.5*</td>
<td>74 ± 6*</td>
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<tr>
<td>Zopolrestat</td>
<td>2 nM</td>
<td>201 ± 3</td>
<td>6.5 ± 0.3</td>
<td>101 ± 4</td>
<td>206 ± 4</td>
<td>4.9 ± 0.3*</td>
<td>67 ± 4*</td>
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<tr>
<td></td>
<td>20 nM</td>
<td>202 ± 11</td>
<td>6.1 ± 0.3</td>
<td>99 ± 3</td>
<td>203 ± 8</td>
<td>4.7 ± 0.4*</td>
<td>65 ± 2*</td>
</tr>
<tr>
<td></td>
<td>200 nM</td>
<td>203 ± 6</td>
<td>6.2 ± 0.4</td>
<td>103 ± 3</td>
<td>203 ± 6</td>
<td>4.8 ± 0.4*</td>
<td>76 ± 5*</td>
</tr>
<tr>
<td></td>
<td>1 μM</td>
<td>203 ± 10</td>
<td>6.0 ± 0.3</td>
<td>95 ± 2</td>
<td>199 ± 9</td>
<td>4.0 ± 0.2*</td>
<td>68 ± 6*</td>
</tr>
<tr>
<td></td>
<td>0.2 nM CB-MECA</td>
<td>210 ± 8</td>
<td>7.4 ± 0.6</td>
<td>102 ± 4</td>
<td>211 ± 10</td>
<td>6.2 ± 0.7*</td>
<td>77 ± 5*</td>
</tr>
<tr>
<td></td>
<td>20 nM zopolrestat + 0.2 nM CB-MECA</td>
<td>213 ± 10</td>
<td>6.7 ± 0.6</td>
<td>98 ± 4</td>
<td>212 ± 12</td>
<td>5.4 ± 0.5*</td>
<td>72 ± 4*</td>
</tr>
</tbody>
</table>

Values are means ± SE. n, no. of rabbit hearts; HR, heart rate; CF, total coronary flow; LVDP, left ventricular developed pressure. *P < 0.05 vs. preocclusion values.
Table 1. LVDP and CF were significantly ($P < 0.05$) reduced in all groups by occlusion of the coronary artery, confirming that ischemia was achieved in all groups. Area at risk expressed as a percentage of left ventricular area ($\%$AAR/LV) was 46 ± 6% ($n = 6$) for the Langendorff control group; the $\%$AAR/LV for the remaining in vitro groups were not significantly different ($P = 0.05$) from the control group.

Zopolrestat elicited a concentration-dependent reduction in infarct size in the isolated rabbit hearts (Fig. 2), with an estimated (because an unequivocal maximum reduction in infarct size was not achieved) EC$_{50}$ of 24 nM. The highest concentration of zopolrestat tested (1 $\mu$M) reduced infarct size by 61% (control, 62 ± 2% IA/AAR; zopolrestat, 24 ± 5% IA/AAR), which was somewhat less than the cardioprotection provided by ischemic preconditioning (12 ± 2% IA/AAR). Sorbitol concentrations (the aldose reductase metabolite of glucose) in the ventricular myocardium were significantly ($P < 0.05$) reduced by 200 nM zopolrestat, whereas 20 nM zopolrestat and 20 nM zopolrestat plus 0.2 nM CB-MECA had no detectable effect (Table 2).

Baseline HR, MAP, and RPP values for each of the in vivo groups were similar (Table 3). The $\%$AAR/LV value for the untreated control group was 55 ± 6%; the $\%$AAR/LV values for the remaining in vivo groups were not significantly different ($P = 0.05$) from the control group.

The effects of zopolrestat (50 mg/kg iv) on MAP, HR, and RPP in the anesthetized rabbit are illustrated in Fig. 3. In the zopolrestat group, there appeared to be a small, transient decrease in MAP during the infusion (preoclusion) and a slightly higher HR compared with vehicle control. However, MAP, HR, and RPP in the zopolrestat-treated group were not significantly different from the vehicle control values when compared over the course of the study. Zopolrestat, at the maximum dose that could be infused, significantly reduced infarct size by 48% (vehicle control, 67 ± 2% IA/AAR; zopolrestat, 35 ± 9% IA/AAR) compared with the 80% reduction observed with ischemic preconditioning (control, 64 ± 3% IA/AAR; ischemic preconditioning, 13 ± 3% IA/AAR) (Fig. 4).

In the isolated heart, a combination of submaximal cardioprotective concentrations of zopolrestat (20 nM) and the adenosine A$_3$-receptor agonist CB-MECA (0.2 nM) (23) produced an additional reduction in infarct size beyond that produced by either agent alone (Fig. 5). The infarct size (20 ± 4% IA/AAR) after this drug combination was similar to that produced by the highest concentration of zopolrestat (1 $\mu$M) when tested alone (24 ± 5% IA/AAR).

**DISCUSSION**

The present study demonstrates that zopolrestat inhibits aldose reductase activity in the rabbit heart and protects the myocardium from ischemia-reperfusion injury. Although the cardioprotective benefit from zopolrestat was somewhat less than that provided by ischemic preconditioning, zopolrestat nonetheless produced a marked concentration-dependent reduction in infarct size in vitro. Moreover, the zopolrestat-dependent reduction in infarct size was also observed in vivo, and the cardioprotection was obtained without significant changes in hemodynamic parameters. The in vivo cardioprotective effect of zopolrestat was substantially less than that provided by ischemic preconditioning, but this protection was limited by the solubility of the compound and the amount that could be infused. Thus, these findings are the first to show that an aldose

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**Table 2. Effect of zopolrestat and zopolrestat plus CB-MECA on sorbitol concentrations in isolated rabbit hearts**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Sorbitol, nmol/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>10</td>
<td>15.0 ± 2.2</td>
</tr>
<tr>
<td>20 nM zopolrestat</td>
<td>4</td>
<td>12.1 ± 1.2</td>
</tr>
<tr>
<td>20 nM zopolrestat + 0.2 nM CB-MECA</td>
<td>4</td>
<td>16.0 ± 2.6</td>
</tr>
<tr>
<td>200 nM zopolrestat</td>
<td>9</td>
<td>6.7 ± 1.3*</td>
</tr>
</tbody>
</table>

Values are means ± SE. n, number of rabbit hearts. Sorbitol concentrations were determined in cardiac tissue after a 5-min perfusion of zopolrestat or zopolrestat + CB-MECA, as described in METHODS. *$P < 0.05$ vs. control.

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**Table 3. In vivo baseline hemodynamic data**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>MAP, mmHg</th>
<th>HR, beats/min</th>
<th>RPP (/100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>7</td>
<td>94 ± 4</td>
<td>288 ± 9</td>
<td>271 ± 14</td>
</tr>
<tr>
<td>Ischemic</td>
<td>7</td>
<td>89 ± 3</td>
<td>264 ± 14</td>
<td>236 ± 19</td>
</tr>
<tr>
<td>preconditioning</td>
<td>6</td>
<td>88 ± 3</td>
<td>292 ± 11</td>
<td>257 ± 16</td>
</tr>
<tr>
<td>Vehicle control</td>
<td>6</td>
<td>90 ± 4</td>
<td>307 ± 11</td>
<td>276 ± 15</td>
</tr>
</tbody>
</table>

Values are means ± SE. n, number of rabbit hearts; RPP, rate pressure product.
Aldose reductase inhibitor can reduce infarct size in nondiabetic experimental animals. Preliminary in vitro studies with a structurally distinct aldose reductase inhibitor, sorbinil, have also demonstrated a comparable degree of cardioprotection (data not shown). In combination with earlier data from isolated diabetic rat hearts (17, 18, 24), these observations implicate the polyol (sorbitol) pathway as an important contributor to myocardial ischemia-reperfusion injury.

Aldose reductase is the first enzyme of the polyol pathway; metabolic flux through this pathway occurs under basal conditions, as evidenced by zopolrestat-dependent suppression of the cardiac sorbitol tissue level (current study) and elevation of the lactate-to-pyruvate ratio (17). Although the mechanism through which polyol pathway inhibition protects the heart from ischemic injury has not been clearly defined, several possibilities exist. Ramasamy and co-workers (17, 18, 24) concluded an important effect of zopolrestat in the ischemic heart was to minimize the increase in the NADH-to-NAD{	extsuperscript{+}} ratio, thereby maintaining glycolysis and limiting ATP depletion. Similarly, ischemic preconditioning also limits the depletion of ATP (and creatine phosphate) (4, 7, 8, 13, 20, 25), suggesting one mechanism that zopolrestat and ischemic preconditioning may share in common. In addition, polyol pathway inhibition may limit NADPH depletion, thereby reducing oxidative stress in the heart, and may sustain...
or increase cardiac nitric oxide production. Both changes would be potentially beneficial, because oxidative stress clearly has a negative impact on myocardial function (1, 3), and nitric oxide (either endogenously produced or from nitric oxide donors) has been reported to reduce myocardial ischemic injury (2, 6, 21, 26). Finally, zopolrestat has been found to increase Na+-K+-ATPase activity and inhibit the rise of intracellular sodium and calcium during ischemia (16).

We have previously shown that stimulation of adenosine A₃ receptors with the selective A₃-receptor agonist CB-MECA reduces infarct size in the isolated rabbit heart (23). Therefore, it was of interest to determine whether a combination of CB-MECA with zopolrestat could produce an additive degree of cardioprotection. A combination of submaximal concentrations of CB-MECA and zopolrestat was found to elicit a reduction in infarct size significantly greater than that produced by either compound individually. Compared with zopolrestat alone, addition of the A₃-receptor agonist allowed a 50-fold reduction in zopolrestat concentration (from 1 μM to 20 nM) while producing a similar reduction in infarct size. Because both zopolrestat (or other aldose reductase inhibitors) and A₃-receptor agonists represent viable therapeutic approaches for clinical cardioprotection, combinations of these agents may be beneficial by either further reducing infarct size beyond that achievable with either agent alone or by allowing a reduction in the dose of these agents.

In conclusion, inhibition of cardiac aldose reductase with zopolrestat protects the myocardium, in vitro and in vivo, from ischemia-reperfusion injury. Moreover, zopolrestat can be combined with a selective A₃-receptor agonist (CB-MECA) to yield additive reductions in infarct size. Thus aldose reductase inhibitors may represent a viable approach to clinical cardioprotection either alone or in combination with other agents.

REFERENCES


