The Cardioprotective Effects of Ischemic 'Preconditioning' Are Not Mediated by Adenosine Receptors in Rat Hearts

Yuwei Li, MD, and Robert A. Kloner, MD, PhD

Background. Adenosine receptor activation has been proposed to explain the cardioprotective effect of ischemic preconditioning in rabbit hearts. We tested this hypothesis in a rat model by assessing whether administration of an adenosine antagonist could block the protective effect of preconditioning and whether adenosine is able to reduce infarct size in rat hearts when given before sustained coronary occlusion.

Methods and Results. We assessed the effects of the adenosine antagonist 8-(p-sulfophenyl)theophylline (SPT) and adenosine on myocardial infarct size and the incidence of ventricular arrhythmias in five groups of rats: control (nonpreconditioned)+vehicle, control+SPT, preconditioned+vehicle, preconditioned+SPT, and control (nonpreconditioned)+adenosine. All rats underwent 90 minutes of coronary artery occlusion followed by 4 hours of reperfusion while preconditioned rats underwent three 3-minute episodes of ischemia, each separated by 5 minutes of reperfusion before sustained occlusion. The area at risk was determined by intravenous injection of blue dye during coronary artery occlusion, and infarct size was determined by incubation of heart slices in triphenyltetrazolium chloride. In the nonpreconditioned control rats receiving vehicle, myocardial infarct size expressed as a percentage of the area at risk averaged 55.2±4.8%. Pretreatment with SPT and adenosine had no effect on infarct size (52.2±3.1% and 52.6±3.8%, respectively) in the nonpreconditioned control animals compared with the control animals that received vehicle. Both the preconditioned+vehicle (16.4±4.3%) and the preconditioned+SPT (18.3±5.2%) groups had a significant reduction in infarct size (p<0.01 versus control+vehicle, control+SPT, and control+adenosine), with no difference in infarct size between the two preconditioned groups. The incidence of ventricular tachycardia was significantly decreased in both the preconditioned+vehicle (10%, p<0.05) and the preconditioned+SPT (25.0%, p<0.05) groups when compared with the control+vehicle (100%), control+SPT (100%), and control+adenosine groups (100%). There was, however, no significant difference in the incidence of ventricular tachycardia between the preconditioned+vehicle and the preconditioned+SPT groups.

Conclusions. Because the adenosine antagonist SPT failed to abolish the cardioprotective effects of preconditioning and intravenous adenosine was unable to protect the hearts, it is unlikely that the mechanism of preconditioning is mediated by adenosine receptors in the rat model. (Circulation 1993;87:1642-1648)

KEY WORDS • ischemia • preconditioning, myocardial • adenosine antagonists • infarcts

The ability of brief periods of ischemia and reperfusion to protect the heart from subsequent more prolonged episodes of ischemia has been termed "preconditioning." The phenomenon of myocardial preconditioning has now been confirmed in the dog, pig, rabbit, and rat and may also exist in humans. However, the mechanism by which preconditioning protects the heart remains unknown. Recently, Liu et al and Thornton et al reported that A1 adenosine receptors mediate the mechanism of preconditioning in rabbit hearts. These authors could block the cardioprotective effect of preconditioning in vivo models by administration of adenosine receptor antagonists and mimic preconditioning in isolated hearts by injection of either adenosine or an A1-selective adenosine receptor agonist. To determine whether the A1 receptor is a mediator of preconditioning in other species, we studied the effects of the adenosine receptor antagonist 8-(p-sulfophenyl)theophylline (SPT) and adenosine in rats. Previous studies in rats have shown that preconditioning can reduce myocardial infarct size and arrhythmias.

Methods

Studies were performed in accordance with guidelines for experimental animals developed by the American Physiological Society. SPT (Research Biochemicals Inc., Natick, Mass.) was dissolved in sterilized water in a concentration of 5 mg/mL; 0.1N NaOH was added to achieve a neutral pH of 7.0–7.4. Adenosine (Research Biochemicals Inc.) was dissolved in saline in a concentra-
TABLE 1. Antagonistic Effect of SPT on Bradycardia Induced by Adenosine in Rats Anesthetized by Pentobarbital or Ketamine and Xylazine

<table>
<thead>
<tr>
<th>Rat No.</th>
<th>Ado (µg/kg)</th>
<th>Before ado</th>
<th>After ado</th>
<th>∆Ado</th>
<th>Before SPT</th>
<th>After SPT, ado</th>
<th>∆SPT, ado</th>
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<tr>
<td>Pentobarbital</td>
<td>1</td>
<td>50</td>
<td>254</td>
<td>195</td>
<td>0</td>
<td>321</td>
<td>197</td>
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<tr>
<td></td>
<td>2</td>
<td>50</td>
<td>231</td>
<td>169</td>
<td>0</td>
<td>231</td>
<td>197</td>
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<tr>
<td></td>
<td>3</td>
<td>100</td>
<td>214</td>
<td>176</td>
<td>0</td>
<td>203</td>
<td>197</td>
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<tr>
<td></td>
<td>4</td>
<td>100</td>
<td>268</td>
<td>170</td>
<td>0</td>
<td>238</td>
<td>185</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>100</td>
<td>221</td>
<td>187</td>
<td>0</td>
<td>221</td>
<td>195</td>
</tr>
<tr>
<td>Mean±SEM</td>
<td>326</td>
<td>8.8±6.4*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketamine/xylazine</td>
<td>1</td>
<td>50</td>
<td>249</td>
<td>245</td>
<td>-184</td>
<td>395</td>
<td>429</td>
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<td>3</td>
<td>100</td>
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<td>273</td>
<td>-76</td>
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<td>1.5±21.0</td>
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To determine whether the dose of 8-(p-sulfophenyl)theophylline (SPT) used could significantly reduce the degree of bradycardia induced by intravenous adenosine (Ado, 50 or 100 µg/kg), we performed the following experiments. Five pentobarbital-anesthetized rats and five ketamine/xylazine-anesthetized rats received 50 or 100 µg/kg of adenosine by intravenous bolus injection. After 10 minutes of recovery, SPT (10 µg/kg) was given as an intravenous bolus followed by a second injection of adenosine (50 or 100 µg/kg). Hemodynamic changes were recorded before treatment with adenosine, immediately after injection of adenosine, before administration of SPT, and immediately after treatment with SPT and adenosine. The changes of heart rate (bpm, beats per minute) from before SPT to after SPT, ado were reported as ∆SPT, ado, which is significantly smaller than the changes induced by adenosine only (Ado) in both pentobarbital-anesthetized (*p<0.02 by paired t test) and ketamine/xylazine-anesthetized rats (†p<0.01 by paired t test). Also, SPT completely prevented the hypotensive response induced by an intravenous bolus of adenosine (50 and 100 µg/kg) in our rat model anesthetized by either pentobarbital or ketamine/xylazine (data not shown). *p<0.05 vs. Ado.

Animal Preparation

Female Sprague-Dawley rats (weight, 320–505 g, n=46) were anesthetized with a combination of ketamine (120 mg/kg) and xylazine (17 mg/kg) administered intramuscularly. Additional anesthesia was given during the experiment as needed. Tracheostomy was performed, and the rats were ventilated with room air using a rodent ventilator (Harvard Apparatus Inc., Natick, Mass.) set at a volume of approximately 1.2 mL/100 g body wt and a rate of 65–68 strokes per minute. Catheters filled with heparinized saline were positioned in the left femoral artery and vein for blood pressure monitoring and drug administration, respectively. The chests were opened by left thoracotomy through the fourth intercostal space, and the pericardium was removed. A suture (6-0 polypropylene) was placed under the left main coronary artery. The thread was then made into an overhand knot (an occluder), and two other threads were tied to the main knot ( releasers). The ends of all threads were brought outside the thoracic cavity. Thus, the occlusion could be tightened or loosened by pulling on the appropriate threads. Myocardial ischemia was confirmed by ST segment changes on the ECG. Lead I of the ECG was monitored throughout the experiment and recorded (50 mm per second chart speed) for ventricular tachycardia (VT) and ventricular fibrillation (VF) when we observed them during the experiment. The experiments were conducted under deep anesthesia, and body temperature was maintained using heating pads.

Experimental Protocol

After the intramyocardial stitch was taken, the rats were randomized to one of four groups at the beginning of the study.

Group 1: control+vehicle. The left main coronary artery was occluded for 90 minutes followed by 4 hours of reperfusion preceded by two injections of vehicle at 30 minutes and 15 minutes before occlusion.

Group 2: control+SPT. Two injections of the adenosine antagonist SPT (10 mg/kg) were given as an intravenous bolus 30 minutes and 15 minutes before the 90 minutes of occlusion. Rats then received 90 minutes of occlusion and 4 hours of reperfusion. We confirmed in 10 additional experiments that this dose of SPT could significantly reduce the degree of bradycardia induced by intravenous adenosine (50 or 100 µg/kg) in sodium pentobarbital–anesthetized rats or ketamine/xylazine–anesthetized rats (Table 1). Moreover, SPT prevented second- and third-degree heart block, which occurred in three rats (two ketamine/xylazine–anesthetized rats and one pentobarbital–anesthetized rat) after administration of adenosine. Also, SPT completely blocked the hypotensive response induced by an intravenous bolus of adenosine (50 or 100 µg/kg) in our rat model anesthetized by either pentobarbital or ketamine/xylazine.

Group 3: preconditioning+vehicle. Three 3-minute periods of ischemia each separated by 5 minutes of reperfusion were used to precondition the myocardium. Rats were then subjected to a sustained 90-minute
occlusion and 4 hours of reperfusion. Vehicle was injected 6 minutes before the onset of the preconditioning regimen and was repeated 15 minutes later.

**Group 4: preconditioning+SPT.** The same regimen was used to precondition the hearts. SPT (10 mg/kg) was administered 6 minutes before the onset of the preconditioning regimen and was repeated 15 minutes later. Because the half-life of SPT is only 10 minutes, two doses were given to maintain high plasma levels of the agent throughout the preconditioning process. The rats then underwent sustained 90-minute occlusion and 4 hours of reperfusion.

We also performed additional experiments to determine whether adenosine or its analogues mimic preconditioning in this model. Rats were randomized to one of three groups: control+vehicle, preconditioning+vehicle, and control+adenosine groups. In the control+adenosine group, rats were treated with a 5-minute intravenous infusion of 1.5 mg adenosine followed by 10 minutes of recovery before a sustained 90 minutes of ischemia. The dose of adenosine was based on a comparable dose given in rabbits.8

At the end of the experiments, the coronary artery was reoccluded, and 1 mL Monastral blue pigment (CIBA-GEIGY) was injected into the left ventricular cavity to determine the area at risk (AR). The rats were then killed under deep anesthesia by injection of potassium chloride, and the hearts were excised. The investigators were blinded to the treatments (vehicle, SPT, or adenosine) during the entire protocol.

**Measurements**

**Hemodynamics.** Measurements of heart rate (five beats were averaged at each time point) and mean arterial pressure (three beats were averaged at each time point) were made in all groups at baseline (i.e., before opening the chest and before treatment), immediately before the sustained occlusion, 30 minutes after occlusion, at the end of the 90-minute occlusion, 60 minutes after reperfusion, and at the end of the experiment.

**Area at risk and area of necrosis.** The hearts were cut into four transverse slices (2–3 mm thick) parallel to the atrioventricular groove, and the heart slices were photographed. The anatomic AR was delineated by the absence of blue dye. The heart slices then were immersed in a 1% solution of triphenyltetrazolium chloride (15 minutes, 35°C). Viable myocardium is stained red by triphenyltetrazolium chloride, whereas necrotic myocardium appears pale yellow, as has been previously validated in the rat model.14 After immersion in triphenyltetrazolium chloride, the heart slices were photographed again. Photographic slides of the heart slices were projected and traced. We marked areas of blue dye (perfused tissue), areas without blue dye (nonperfused tissue), and areas of infarcted and uninfarcted myocardium. The AR and area of necrosis (AN) in each heart slice were determined by computerized planimetry, corrected for tissue weight, and summed for each heart.9 The AN in each heart was then expressed as a percentage of the AR of necrosis (AN/AR). Rats with an AR <10% of the left ventricle were excluded from the study.

**Arrhythmia.** The primary end point of this study was infarct size. However, we also analyzed records of the ECG for the incidence of VT and VF. VT in our experiment was defined as the occurrence of three or more consecutive ectopic beats. Because the ECG was recorded only when arrhythmias were apparent to the investigator, we did not determine the frequency and duration of ventricular ectopy.

**Statistics**

The measurements of hemodynamics, AR, and AN are expressed as group mean±SEM values. The data for arrhythmia during the 90 minutes of occlusion are reported as incidence. Two-way ANOVA was used for comparisons of the hemodynamics. For AR and AN data, one-way ANOVA was used to determine whether there were differences among the five groups, and Tukey's test then was used to determine pairwise differences between groups. Differences among groups for the arrhythmia data were assessed by χ² and Fisher's exact test: χ² was used to test the difference among the five groups, and Fisher's exact was used to determine pairwise difference. A value of p<0.05 was considered statistically significant.

**Results**

**Mortality and Exclusions**

A total of 63 rats were entered into the protocol. Seven died perioperatively. Three rats were excluded from the study because of an inability to reperfuse the infarcts. In these three rats, the stitch passed through the coronary artery, causing excessive bleeding and an inability to reperfuse; these rats were immediately euthanized under deep anesthesia by injection of potassium chloride. In four rats, injection of blue dye was suboptimal, and these rats were eliminated from the data. Three rats were excluded on the basis of AR<10% of the left ventricle. Thus, data of 46 rats from the experiments (12 rats in the control+vehicle group, eight rats in the control+SPT group, 10 rats in the preconditioned+vehicle group, eight rats in the preconditioned+SPT group, and eight rats in the control+adenosine group) are included in this study.

**Hemodynamics**

The hemodynamic data for all of the groups are summarized in Table 2. Heart rate fell between baseline (closed chest) and opening the chest for the intrathoracic procedure. Mean blood pressure did not change from baseline (closed chest) to preconditioning values. After the onset of myocardial infarction, there was a trend for blood pressure and heart rate to fall in all groups. However, there were no significant differences in either heart rate or arterial blood pressure among the five groups after coronary occlusion. The infusion of adenosine significantly reduced the heart rate and the mean arterial pressure compared with the control+vehicle group randomized at the same time. The heart rate in the adenosine group was 116±10 beats per minute at the end of infusion versus 178±17 beats per minute in the control group (p<0.05 by group t test, Figure 1), and the mean arterial pressure was 56±6 mm Hg in the adenosine group versus 83±7 mm Hg in the control group (p<0.05).

**Area at Risk and Area of Necrosis**

The anatomic AR expressed as a percentage of the left ventricle was comparable in all of the groups: 43.9±5.0%
Li and Klener  Preconditioning and Adenosine Receptors  1645

in the control+vehicle group, 45.8±2.8% in the control+SPT group, 50.3±3.9% in the preconditioned+vehicle group, 36.2±5.1% in the preconditioned+SPT group, and 53.1±3.7% in the control+adenosine group (p=NS among the groups). See Figure 2.

Myocardial infarct size expressed as a percentage of the anatomic AR in control rats that received vehicle averaged 55.2±4.8%. Pretreatment with SPT had no effect on infarct size in control animals (52.2±3.1%). Infarct size in preconditioned+vehicle rats (16.4±4.3%) and preconditioned+SPT rats (18.3±5.2%) was significantly lower than in either group of nonpreconditioned rats (p<0.01). There was no difference in infarct size between the preconditioned rats receiving vehicle versus the preconditioned rats receiving SPT. Pretreatment with intravenous infusion of 1.5 mg adenosine before ischemia did not produce a reduction of infarct size (52.6±3.8%, p>0.01 versus preconditioned rats and p=NS versus control rats).

Incidence of Ventricular Arrhythmias

The incidence of arrhythmias during the brief episodes of the preconditioning period was low: One preconditioned+SPT rat had VT in the third occlusion period. During the 90 minutes of coronary occlusion, VT developed in all control+vehicle, control+SPT, and control+adenosine animals and in one rat in the preconditioned+vehicle group and in two rats in the preconditioned+SPT group. Thus, the incidence of VT in both the preconditioned+vehicle group (10%) and the preconditioned+SPT group (25%) was significantly decreased (p<0.05 compared with control+vehicle, control+SPT, and control+adenosine). However, there was no difference in the incidence of VT between the

FIGURE 1. Graph shows that the intravenous infusion of adenosine significantly reduced the heart rate compared with the control+vehicle group randomized at the same time. The heart rate in the adenosine group was 116±10 beats per minute at the end of infusion versus 178±17 beats per minute in the control group (p<0.05 by group t test).

FIGURE 2. Bar graph showing the effect of 8-(p-sulfophenyl)theophylline (SPT) and adenosine on myocardial infarct size in rats. Infarct size is expressed as a percentage of the risk zone (area of necrosis/area at risk, AN/AR%; columns are group means and bars are SEM). *p<0.01 for preconditioned+vehicle (P) and preconditioned+SPT (P+SPT) groups versus control+vehicle (C), control+SPT (C+SPT), and control+adenosine (C+ADO) groups by ANOVA/Tukey's test. SPT did not significantly change the infarct size in either control or preconditioned rats compared with vehicle, and intravenous adenosine had no effect on infarct size induced by 90 minutes of occlusion. Area at risk expressed as a percentage of the left ventricle (AR/LV%) was similar in all of the groups.
preconditioned+vehicle and preconditioned+SPT groups. VF occurred in six rats (50%) in the control+vehicle group, in three rats (37.5%) in the control+SPT group, and in one rat (12.5%) in the control+adenosine group. No VF occurred in either preconditioned+vehicle or preconditioned+SPT groups. The incidence of VF did not reach statistical significance among the groups. C, control; P, preconditioned.

To determine whether a higher dose of adenosine receptor antagonist could block the protective effects of preconditioning, we also studied the effect of SPT (25 mg/kg) in three additional preconditioned rats. We found that all three rats had a small infract size (13.7±4.6%) compared with the nonpreconditioned control rats; no rats exhibited VT and VF during the sustained 90 minutes of coronary artery occlusion. Therefore, even higher doses of SPT failed to eliminate the beneficial effects of preconditioning in this model.

**Discussion**

The results from the present study confirm that preconditioning with three cycles of 3 minutes of ischemia, each interrupted by 5 minutes of reperfusion, reduced infract size produced by a subsequent 90 minutes of coronary occlusion in the rat model. We did not, however, confirm the role of adenosine as a mechanism for ischemic preconditioning. Pretreatment with the adenosine receptor antagonist SPT did not affect infract size in either control or preconditioned rats. The incidence of VT was significantly decreased in both the preconditioned+vehicle and preconditioned+SPT groups when compared with control groups. Because preconditioning protected the myocardium from necrosis regardless of treatment with SPT, it is unlikely that the mechanism of preconditioning can be attributed to adenosine receptors in our rat model.

In addition, a large dose of adenosine failed to protect the rat heart, as seen with preconditioning in this study. Although it has been reported previously that intravenous adenosine was not sufficient to achieve a protective concentration in coronary circulation in in situ rabbit hearts because of widespread peripheral dilatation and its subsequent marked hypotension, Toombs et al. found a significant reduction of infract size by intravenous infusion of adenosine in their rabbit model of 30 minutes ischemia, which was independent of hemodynamic effects. The reason for the discrepancy is unclear. In a preliminary study, we also examined an A1-selective adenosine analogue A2B(2-phenylisopropyl)-adenosine (PIA) with four different doses: 1 mg/kg, 0.5 mg/kg, 0.25 mg/kg, and 0.1 mg/kg. However, the rats were unable to tolerate these doses of PIA because of the severe bradycardia and hypotension.

Recent studies have provided evidence disproving some of the initial hypotheses that were proposed to explain preconditioning such as oxygen-derived free radical scavengers,16-18 myocardial stunning,19,20 heat shock protein,21-23 and prostacyclin.24,25 Another recent proposal is that preconditioning is associated with a decrease in rate of ATP depletion.26 This has been attributed to activation of an oligomycin-sensitive mitochondrial ATPase inhibitor that is thought to represent a major cause of ATP degradation during ischemia.37 However, the absence of functional mitochondrial ATPase inhibitor in the rat,28 a species in which preconditioning has been shown to occur, does not support this hypothesis. Recently, an alternate mechanism has been proposed that myocardial protection afforded by preconditioning was prevented by blockade of ATP-sensitive K+ channels in the dog.29 However, ATP-sensitive K+ channels do not appear to mediate preconditioning in the rabbit heart,30 despite the fact that A1 adenosine receptors and ATP-sensitive K+ channels are coupled at the surface of cardiac cells.31

Adenosine has been described as a cardioprotective molecule.32 Its protective role in myocardial ischemia may be achieved by regulating the myocardial oxygen supply–demand balance. During the period of oxygen deprivation, adenosine increases energy production through increased glycolytic flux and during reperfusion revives cellular energy charge via purine salvage pathways.32 Intracoronary administration of adenosine after reperfusion has been shown to significantly reduce infract size, improve regional ventricular function, decrease neutrophil infiltration, and preserve the ultrastructure of vascular endothelial cells in the canine model.33,34 Recently, intravenous infusion of adenosine in the early reperfusion period was observed to attenuate myocardial infract size in either the canine model or rabbit model.35,36 These investigators also studied A1 and A2 adenosine receptor agonists in rabbit hearts subjected to 30 minutes of coronary occlusion and 48 hours of reperfusion. They found that both adenosine receptor agonists afforded comparable degrees of cardioprotection and suggested that this protection is receptor mediated.37 In isolated rat hearts, adenosine has been reported to stimulate glycolysis in both the normoxic and hypoxic myocardium38 and prolong the time to onset of myocardial ischemic contracture via an adenosine A1 receptor mechanism.39

The hypothesis that ischemic preconditioning may be mediated through activation of A1 adenosine receptors by adenosine produced in the preconditioning episode was first examined in the rabbit heart by Liu et al.8 These authors observed that 1) two adenosine receptor blocking agents, SPT and PD115199, abolished the
protective effect of preconditioning, and 2) a 5-minute intracoronary infusion of adenosine and A1-specific agonist R-PIA substituted for the protective effect of preconditioning in the isolated heart. Recently, intravenous pretreatment with A1-selective adenosine analogues and adenosine has been shown to be as effective in limiting myocardial infarct size as preconditioning.14,15 Unfortunately, the exact intracellular pathway(s) through which activation of A1 adenosine receptors might protect the myocardium is not known.

However, this adenosine preconditioning hypothesis is not supported by the present results; SPT did not prevent or attenuate the protective effect of preconditioning. Although we cannot offer a definitive explanation, numerous factors might contribute to the apparent discrepancy with the data of Liu et al: 1) differences in the preconditioning regimen, 2) difference in the duration of sustained occlusion, and 3) possible differences between rats and rabbits. An additional explanation for these conflicting results is that the mechanism of preconditioning in the rat may involve a subtype of adenosine receptors that are not responsive to SPT. Moreover, preliminary evidence suggests that adenosine did not mimic preconditioning (did not preserve contractile function) in the globally ischemic isolated rat heart.40 A recent study from our laboratory by Hale et al showed that intracoronary infusion of high-dose adenosine did not mimic preconditioning in in vivo rabbit hearts (unpublished data).

We conclude from our data that preconditioning either with or without the adenosine receptor antagonist SPT significantly reduced the volume of infarcted myocardium and protected against VT in rat hearts that had undergone 90 minutes of coronary occlusion and 4 hours of reperfusion. Because the adenosine receptor antagonist failed to eliminate the cardioprotection of preconditioning and high-dose intravenous adenosine was unable to limit myocardial infarct size, adenosine receptors are unlikely to play a major role in the mechanism of ischemic preconditioning in the rat model.

Acknowledgment

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