Attenuation of No-Reflow Phenomenon, Neutrophil Activation, and Reperfusion Injury in Intestinal Microcirculation by Topical Adenosine

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Small mesenteric arteries supplying partially isolated jejunal segments were totally occluded for 5 minutes and then released. With video microscopy, blood flow was calculated from measurements of submucosal arteriolar diameter and red blood cell velocity. For the first 30 minutes of reperfusion, the serosa was superfused with a Ringer's vehicle containing either adenosine (ADO; 10\textsuperscript{-4} M), acetylcholine (ACh; 10\textsuperscript{-7} M), or prostacyclin (PGI\textsubscript{2}; 3×10\textsuperscript{-7} M). Thereafter, the substances were removed from the suffusate, and superfusion continued with vehicle alone for an additional 10–30 minutes. These concentrations were equieffective for causing vasodilation. During the first minute of reperfusion, blood flow increased more than 300% of baseline in all groups. Within the subsequent 30 minutes, blood flow fell to 45±3% of baseline with vehicle alone, which demonstrates the no-reflow phenomenon. While either ADO, ACh, or PGI\textsubscript{2} was in the suffusate, vasodilation was persistent. After washout of these substances, the postocclusion blood flows were significantly higher with each treatment than with vehicle alone, which shows that each substance had a positive action. However, with ADO, blood flow was 121±7% of baseline after washout, whereas with ACh or PGI\textsubscript{2}, it was 64±10% or 69±5% of baseline after washout. This property of ADO was observed if the mucosa was superfused with a Ringer's solution or with a bile salt solution, which suggests that ADO might have similar properties in situ. After 60 minutes of reperfusion, the intestinal villi were short, thick, and edematous with epithelial necrosis and crypt degeneration. ADO attenuated most of these histological changes to a greater extent than either PGI\textsubscript{2} or ACh. Furthermore, ADO reduced a biochemical index of neutrophil infiltration; tissue myeloperoxidase concentration was increased to 169±14% of baseline with vehicle but was increased to 120±8% with ADO. Overall, these observations suggest that ADO protects the intestine from ischemia-reperfusion injury by causing vasodilation and by inhibiting neutrophil function. The vasodilatory effect probably is a minor component because other vasodilators (ACh and PGI\textsubscript{2}) had minimal protective effects in these conditions. (Circulation Research 1989;65:426–435)

The intestine is one of the tissues most sensitive to ischemia-reperfusion injury.\textsuperscript{1} After brief periods of occlusion, reperfusion is associated with nonuniform, incomplete restoration of nutrient blood flow to large regions of the microcirculation.\textsuperscript{2} This "no-reflow phenomenon" is probably caused by arteriolar vasoconstriction and by plugging of capillaries with invading neutrophils, platelets, and cell fragments.\textsuperscript{3} In addition, the integrity of the vascular endothelium is destroyed, which leads to widespread tissue edema.\textsuperscript{1,2,4} Several factors participate in ischemia-induced changes in the intestine, including cytotoxic and vasoconstrictor substances released from invading leukocytes (O\textsubscript{2} radicals, leukotrienes, proteases, etc.), platelets (thromboxane, serotonin, etc.), and damaged resident cells (histamine, kinins, etc.). Furthermore, ATP is depleted during the ischemic period, so the tissue's energy balance is disturbed.

Several properties of adenosine are potentially beneficial during ischemia-reperfusion injury, including vasodilation, inhibition of O\textsubscript{2}-radical generation by leukocytes and vascular endothelium, and inhibition of leukocyte chemotaxis (e.g., see References

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5–7). These actions could account for the beneficial effect of adenosine in coronary ischemia-reperfusion injury.7,8 The purpose of these experiments was to compare the effect of adenosine with that of structurally dissimilar vasodilators on ischemia-reperfusion injury in the intestinal microcirculation.

Materials and Methods

General

Male Sprague-Dawley rats (170–300 g) were anesthetized with an aqueous mixture containing 13% urethane and 1% α-chloralose (1.0 ml/100 g body wt i.p.). Supplemental doses were administered when necessary (0.1 ml/100 g body wt i.v.). The trachea, femoral artery, and femoral vein were cannulated. Respiration was spontaneous on room air supplemented with 100% O2. Rectal temperature was continuously monitored (Yellow Springs Instr. International, Yellow Springs, Ohio) and maintained at 36–37°C with a heat lamp. Femoral arterial blood pressure was continuously monitored with a transducer (P23ID, Gould-Statham, Oxnard, California) connected to a six-channel polygraph (model 2600, Gould) and typically ranged between 90 and 110 mm Hg for the 3–4-hour duration of the experiment.

Microcirculatory Preparation

A 1–2-cm section of the jejunum was prepared, with several modifications9–11 of a previously described technique.12 Briefly, a segment of jejunum was drawn through a surgical opening in the abdominal wall. Several ties were sutured adjacent to the antimesenteric border. A longitudinal incision was made between the suture rows with a microcautery. The upper flap of tissue was retracted, or if systemic arterial blood pressure decreased excessively, if a preparation lacked vasomotor tone, or if systemic arterial blood pressure decreased below 70 mm Hg.

Ischemic injury to the partially isolated intestinal segment was produced by clamping the small mesenteric arteries that supplied the exposed tissue. After 5 minutes, the clamp was released. Throughout the protocol, the mucosa and serosa were continuously superfused at 3–7 ml/min. For the first 30 minutes of reperfusion, either ADO (10–4 M), acetylcholine (ACH; 10–5 M; Sigma) or prostacyclin (PGI2; 3 × 10–7 M; gift from Dr. Salvador Moncada, Burroughs Wellcome, Beckenham, Kent, England) was added to the serosal suffusate. That substance was then removed, and suffusion continued for an additional 10–30 minutes with the bicarbonate-buffered Ringer’s vehicle only.

In a few control experiments, the test substances were applied to the serosa of uninjured tissue for 30 minutes followed by a 10–30-minute suffusion with vehicle only.

In most experiments, the mucosa was suffused with the vehicle alone. In some experiments, the mucosa was suffused with 10 mM bile salt (i.e., taurocholic acid; Sigma) in vehicle to mimic luminal contents in vivo.
Histology

Tissue samples were harvested at the end of the microcirculatory experiments and were preserved with an aqueous solution containing 1.5% glutaraldehyde (Sigma) and 1% paraformaldehyde (Sigma) for 15 minutes, as previously described.14 The tissue was stored in 10% buffered formalin (Sigma) for 12–24 hours. The specimen was then embedded, sectioned, and stained with hematoxylin and eosin according to standard light microscopy techniques. Villus length, villus width, crypt depth, and mucosa thickness were measured in the fixed, stained specimens with the video microscope system.

Biochemical Assay

To estimate the amount of infiltrating leukocytes, tissue myeloperoxidase concentration was measured with a previously described method.15,16 Briefly, tissue samples were weighed and homogenized (Polytron, Brinkmann Instruments, Westbury, New York) in 0.2 M KH₂PO₄, pH 7.4, Mallinkrodt, Paris, Kentucky). A 7-ml aliquot of the homogenate was centrifuged (16,000 rpm, 20 minutes, 4°C). The supernatant was discarded, and the pellet was rehomogenized in 5 ml 0.05 M KH₂PO₄ (pH 6.0) containing 0.5% hexadecyltrimethylammonium bromide (HETAB; Sigma). HETAB is a detergent that releases myeloperoxidase from the primary granules of the neutrophil.16 The rehomogenized cell suspension was freeze-thawed two times and sonicated on ice for 60 seconds (Kontes Micro-ultrasonic Cell Disrupter, Vineland, New Jersey). The diluted sample (0.1 ml) was combined with 0.08 M KH₂PO₄ containing 0.1 ml 0.016 M 3,3′,5,5′-tetramethyl benzidine (TMB; Sigma) and 0.03 M H₂O₂ (Mallinkrodt).

The myeloperoxidase concentration in each sample was determined by measuring the H₂O₂-dependent oxidation of TMB. The change in absorbance was measured at 655 nm and 37°C C Instruments, (model DV40 Spectrophotometer, Beckman Instruments, Norcross, Georgia). Absorbance was converted to protein concentration per gram of tissue from a standard curve, in which peroxidase (type VI, Sigma) was substituted for myeloperoxidase, as previously described.16

Myeloperoxidase concentration was assayed in two groups in which the mesenteric arteries feeding a 2-cm segment of jejunum were occluded for 5 minutes and then released. In the first group, the tissue was continuously bathed with the vehicle during 60 minutes of reperfusion. In the second group, ADO was added to the bathing solution for the first 30 minutes of reperfusion followed by an additional 30 minutes of reperfusion in which the tissue was bathed with vehicle only. In each animal, one sample was harvested from the ischemic jejunum, and one sample was harvested from an adjacent well-perfused section of the jejunum in which the arterial supply had been undisturbed. Three dilutions were made of each tissue sample, and duplicate measurements were made at each dilution. Thus, there were two tissue samples per experimental animal and six absorbance measurements on each tissue sample. In our laboratory, duplicate measurements of absorbance varied less than 3% (n=77).

For each treatment group, the myeloperoxidase concentration in the reperfused tissue was compared with that in the adjacent tissue whose blood flow had been undistributed.

Statistical Analysis

All values are expressed as mean±SEM. All treatments were randomized, and some measurements were paired. Differences were determined with analysis of variance and paired or unpaired t tests. Significance was assessed at the 95% confidence interval.

Results

In pilot experiments, either ADO (10⁻⁴ M; n=2), ACh (10⁻⁵ M; n=2) or PGI₂ (3x10⁻⁷ M; n=1) was topically applied to the serosa for 30 minutes, then washed out. The mucosal suffusate contained Ringer's-bicarbonate buffer only. Vascular supply to these preparations was not occluded. Within 1–2 minutes, each substance produced an increase in submucosal arteriolar diameter (120–140% of baseline) and calculated blood flow (200–300% of baseline) that was sustained for the 30 minutes of treatment. Within 10 minutes after the substances were removed from the suffusate, diameter and blood flow stabilized at the pretreatment baseline and remained at that level for at least 40–60 minutes. These data show that a 30-minute topical application of these various substances at these concentrations had no persistent effect on the microcirculation.

Table 1 shows the responses evoked by the serosal application of the three vasodilators on arteriolar diameter and calculated blood flow after occlusion of a small mesenteric artery. The vasodilators were topically applied for the first 30 minutes of reperfusion, and data were collected until the hemodynamic variables stabilized at a postocclusion baseline (10–30 minutes after washout at minutes 40–60 of reperfusion). These data show that 1) reactive hyperemia of similar magnitude occurred on reperfusion in each group; 2) the duration of the reactive hyperemia was prolonged if the serosal suffusate contained a vasodilator, but the hyperemia was transient if the suffusate contained vehicle only; 3) within 10–30 minutes after washout of the vasodilators, blood flow stabilized at lower levels; 4) these postocclusion values in the ACh- and PGI₂-treated groups were higher than the values in the vehicle group but lower than the values in the ADO-treated group.

Before occlusion, the steady-state baselines for arteriolar diameter and calculated blood flow ranged from 60–66 μm and 28–35 ml/sec in the four groups of animals and were not significantly different.
There were no systemic changes in arterial blood pressure caused by occlusion of the small mesenteric arteries or by the local application of the vasodilators.

With vehicle only in the serosal suffusate, diameter and blood flow rose to 150±5% and 360±35% baseline during the first few minutes of reperfusion. The increases were transient; within 30 minutes, diameter and blood flow significantly decreased below the preocclusion steady state (83±2% and 48±3% of baseline) and remained depressed until the end of the 40–60-minute reperfusion period. These results demonstrate the no-reflow phenomenon in this experimental model.

With ADO in the serosal suffusate for the first 30 minutes of reperfusion, arteriolar blood flow initially increased to 369±38% of baseline, which was similar to the initial blood flow increase in the vehicle group. Thereafter, blood flow declined to 202±44% of baseline for the remainder of the 30-minute treatment period. Within 10–30 minutes after ADO was washed out, blood flow decreased to 121±7% of baseline, which was significantly higher than the preocclusion value. Thus, topical ADO prevented the no-reflow phenomenon in these experimental conditions.

With ACh treatment for the first 30 minutes of reperfusion, the diameter and blood flow increases at the first and 30th minute were essentially identical to those in the ADO group. On washout of ACh, diameter and blood flow decreased to 86±4% and 64±10% of baseline, which were significantly lower than the preocclusion control and significantly lower than the postocclusion diameter and blood flow in the ADO group. Nevertheless, ACh treatment significantly attenuated the no-reflow phenomenon because postocclusion blood flow was higher than that in the vehicle-treated group.

While PGI₂ was in the serosal suffusate, the diameter and blood flow changes during the 30 minutes of treatment were essentially identical to those in the other two treatment groups. After washout of PGI₂, diameter fell to 88±6% of baseline, which was not significantly different than preocclusion. However, blood flow stabilized at 69±5% of baseline, which was significantly lower than the preocclusion value and significantly lower than the corresponding postocclusion blood flow in the ADO group. Nevertheless, PGI₂ treatment did attenuate the no-reflow phenomenon because the postocclusion blood flow was significantly higher than that in the vehicle group.

Table 2 shows that topical ADO prevented the no-reflow phenomenon in slightly different experimental conditions. In this control group, the mucosal suffusate contained a solution of bile salt in vehicle, and the serosal suffusate contained the vehicle only. In these animals, baseline arteriolar diameter and calculated blood flow, and the responses during reperfusion were essentially identical to those values in the larger sample population with vehicle suffusing both the serosa and mucosa (see Table 1). With bile salt on the mucosa, preocclusion blood flow increased during the first minute of reperfusion, and then eventually stabilized after 40–60 minutes of reperfusion at 36±7% of baseline, which was significantly below the preocclusion value.

With bile salt suffusing the mucosa, preocclusion blood flow in the ADO-treated group increased during the first minute of reperfusion. After washout of ADO, postocclusion blood flow stabilized at 141±7% of baseline, which was significantly higher than the original baseline. Thus, serosal ADO prevented the no-reflow phenomenon even if the mucosa was suffused with bile salt.
TABLE 2. Effect of Adenosine on Arteriolar Diameter and Calculated Arteriolar Blood Flow Before and After Occlusion of a Small Mesenteric Artery With Bile Salt in Mucosal Suffusate

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<th>Preocclusion baseline</th>
<th>Reperfusion period</th>
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<tr>
<td></td>
<td>Diam BF</td>
<td>Diam BF</td>
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<tr>
<td>Vehicle (n=4)</td>
<td>60±1</td>
<td>33±4</td>
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<tr>
<td>ADO (n=6)</td>
<td>61±4</td>
<td>36±3</td>
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All values are mean±SEM.

Diam, arteriolar diameter in microns; BF, arteriolar blood flow calculated in nanoliters per second from diameter and red blood cell velocity (not shown); n, number of animals; vehicle, bicarbonate-buffered Ringer’s solution; mucosal suffusate consisted of bile salt (10 mM taurocholic acid) in vehicle; serosal suffusate consisted of either vehicle alone or adenosine (ADO; 10⁻⁴ M) in vehicle.

*Adenosine in serosal suffusate for first 30 minutes of reperfusion.
†Significant difference from preocclusion baseline.
‡Significant difference from vehicle.

Figure 1 graphically compares the effects of vasodilator treatment on postocclusion arteriolar blood flow (expressed as percent of the steady-state preocclusion baseline) with the mucosa suffused with vehicle only (Panel A) and with the mucosa suffused with vehicle plus bile salt (Panel B). These data represent the normalized responses from Tables 1 and 2. With vehicle superflushing the mucosa and the serosa, blood flow was reduced to 45±3% of baseline after 40-60 minutes of reperfusion. In the ACh- and PGI₂-treated animals, postocclusion blood flow was reduced 64±10% and 69±5% of baseline. These values were significantly higher than the value with vehicle only, even though they were depressed below the preocclusion baseline. In contrast, with ADO treatment, postocclusion blood flow was significantly higher (121±7% of baseline) than the preocclusion control and the values in the other two treated groups.

With the mucosa suffused with vehicle plus bile salt and the serosa suffused with vehicle alone (Panel B), postocclusion blood flow was significantly reduced below the preocclusion baseline. If ADO was added to the serosal suffusate for the first 30 minutes of reperfusion, postocclusion blood flow stabilized at a level that was significantly higher than the preocclusion baseline and significantly different from the value with vehicle alone.

In summary, the results in Tables 1 and 2, and Figure 1 show that serosal application of PGI₂ and ACh attenuated, whereas ADO prevented, the no-reflow phenomenon and that the efficacy of ADO...
Figure 2. Effect of adenosine (ADO) on tissue myeloperoxidase concentration after 60 minutes reperfusion. If ADO was added to the serosal suffusate for the first 30 minutes of reperfusion, tissue myeloperoxidase after 60 minutes of reperfusion was significantly increased above the preocclusion baseline. However, the value in the ADO group was significantly lower than the corresponding value in the vehicle group.

Figure 3 illustrates hematoxylin and eosin-stained specimens of vehicle-suffused tissue before and after ischemia-reperfusion injury (magnification, ×40). Panel A shows the histological appearance of the tissue before occlusion. Panel B shows a similar tissue segment after 5 minutes of ischemia and 60 minutes of reperfusion. It is obvious that the villi are shorter, thicker, and edematous. There are

was not altered by a mucosal solution containing bile salt.

Figure 2 shows the effect of ADO on tissue myeloperoxidase concentration. In uninjured tissue that was exteriorized and superfused for 60 minutes with vehicle, myeloperoxidase concentration averaged 3.1±0.2 mg protein/g tissue (n=13). This value was considered “baseline” in these experimental conditions. After 5 minutes of occlusion and 60 minutes of reperfusion, myeloperoxidase concentration was significantly elevated to 4.6±0.6 mg protein/g tissue (169±14% of baseline). After 60 minutes reperfusion in the ADO-treated group, tissue myeloperoxidase was 4.0±0.4 mg protein/g tissue (120±8% of baseline), which was significantly higher than the myeloperoxidase level before occlusion but significantly lower than the concentration in the vehicle-treated tissue after 60 minutes of reperfusion. Thus, ADO reduced, but did not prevent, the ischemia-induced increase in myeloperoxidase concentration.

Figure 3 illustrates hematoxylin and eosin-stained specimens of vehicle-suffused tissue before and after ischemia-reperfusion injury (magnification, ×40). Panel A shows the histological appearance of the tissue before occlusion. Panel B shows a similar tissue segment after 5 minutes of ischemia and 60 minutes of reperfusion. It is obvious that the villi are shorter, thicker, and edematous. There are
areas of epithelial necrosis, especially at the tops of the villi, and a decreased depth of the crypts at the base of the villi. In the submucosa and serosa, note the granular degeneration with edema and partial separation between the tissue layers. It is important to emphasize that these sections were obtained after only 60 minutes of reperfusion. It is reasonable to expect more severe structural damage after longer periods of reperfusion. Closer inspection of the tissue revealed that only a moderate number of neutrophils had infiltrated the tissue at this early stage after the injury. Panel C shows a jejunal segment after 30 minutes of occlusion and 60 minutes of reperfusion; note the progression of damage, compared with Panel B.

Figure 4 illustrates tissue that had been treated for the first 30 minutes of reperfusion with three structurally dissimilar vasodilators. Panel A shows the effect of ADO; the villi are shorter than those in uninjured tissue (Figure 3A) but much taller than those in injured, vehicle-treated tissue (Figure 3B). Note further that in the ADO-treated tissue, there is less separation between the serosa and mucosa and that the crypts at the base of the villi are more preserved. The full protective effect of ADO was not shared by the other vasodilators. After ACh (Figure 4B) and PGI2 (Figure 4C), there was less epithelial necrosis than in the vehicle-treated specimens, but there were signs of more edema, and the villi were shorter and thicker than in the ADO-treated sample.

Figure 5 presents quantitative histology data. Panel A shows that villus length averaged 334±20 μm before occlusion with vehicle suffusion. After 5 or 30 minutes of ischemia followed by 60 minutes of reperfusion, villus length was significantly shortened. With ADO treatment, villus length averaged 255±24 μm, which was significantly higher than villus length with vehicle or the other two treatments. Nevertheless, ADO did not completely prevent the ischemia-induced shortening of the villus.

Panel B shows that villus width averaged 98±5 μm before occlusion with vehicle suffusion. After injury, villus width was significantly increased in vehicle-treated tissue, which implies villus edema. With ADO treatment, villus width was maintained at 102±5 μm after injury, which was significantly less than that in vehicle group after injury. Widths averaged 118 and 112 μm in the ACh and PGI2 groups, respectively, which were not statistically different from the ADO value. Thus, all three treatments tended to prevent the ischemia-induced swelling of the villus.

Panel C shows that ADO treatment preserved crypt depth after ischemic injury. Before occlusion, crypt depth was 134±2 μm and decreased to 104–108 μm after ischemia-reperfusion with vehicle suffusion. With ADO treatment, crypt depth averaged 132±15 μm after injury. With ACh or PGI2 treatment, the values were significantly lower (83–99 μm).

Panel D shows the total mucosa thickness decreased from 485±26 μm before occlusion to
FIGURE 5. Effect of the various treatments on villus length, villus width, crypt depth, and mucosa thickness. Note that reperfusion injury was characterized by short, thick villi, with crypt degeneration, and a decrease in mucosal thickness. Adenosine (ADO) attenuated or prevented most of these changes, and its effect was more pronounced than the effects of either acetylcholine (ACh) or prostacyclin (PGI₂).

252±10 μm after ischemia-reperfusion with vehicle suffusion. The values were similar in the ACh-treated (256±12 μm) and PGI₂-treated (253±16 μm) groups. With ADO, the value (390±37 μm) was not fully restored to the preocclusion baseline, but it was significantly greater than mucosa thickness in the other treatment groups.

In summary, the results in Figures 3–5 show that ischemia-reperfusion injury caused a generalized destruction of the mucosa that included shortening and thickening of the villi and destruction of the crypts at the base of the villi. ADO attenuated most of these changes to a greater extent than either ACh or PGI₂.

Discussion

Topical adenosine prevented the no-reflow phenomenon (Table 1, Figure 1), reduced the increase in tissue myeloperoxidase concentration that accompanied reperfusion (Figure 2), and attenuated the histological changes associated with reperfusion (Figures 3–5) in partially isolated jejunal segments that were superfused with a Ringer's-bicarbonate buffer. Ischemic injury was aggravated with bile salt added to the lumenal suffusate, but adenosine was even more effective in these experimental conditions (Figure 1, Table 2).

It should be emphasized that adenosine was topically applied to the serosa in this study, even though the metabolically active mucosa is more sensitive to ischemic injury. Adenosine was applied to the serosa because the mucosa presents a physical and metabolic diffusion barrier that limits the passage of adenosine from the lumen to the interstitium. Nevertheless, the data in Figures 3–5 strongly suggest that adenosine must have penetrated from the serosa to the mucosa because the histological characteristics of reperfusion injury were significantly attenuated by serosal application.

Other experimental conditions also deserve comment. The various test substances were topically applied for the first 30 minutes of reperfusion and then washed out of the suffusate. This treatment interval was selected because previous studies sug-
gest that much of the injury process begins during the early stages of reperfusion. The present results show that this treatment interval was indeed effective. On the other hand, neither the long-term effects of 5 minutes of occlusion nor the long-term efficacy of these treatments was evaluated.

There is now little doubt that O2-derived free radicals are important mediators of the cell injury produced by reperfusion of ischemic intestine. These highly reactive metabolites are derived from at least two sources: tissue (i.e., endothelial and epithelial) xanthine oxidase and neutrophilic NADPH oxidase. Besides acting as an immediate source of O2 radicals, the invading neutrophils release numerous cytotoxic and proinflammatory mediators. Furthermore, the adherence of neutrophils to damaged endothelium causes capillary plugging that physically contributes to the no-reflow phenomenon. After activated neutrophils have adhered to injured capillary endothelium, the generation of chemotactic factors recruits more neutrophils to the site, which initiates a positive feedback system that exacerbates the injury and ultimately results in cell death. Thus, there is general agreement that activated neutrophils and O2 radicals contribute to intestinal ischemia-reperfusion injury.

Adenosine inhibits the generation of O2 radicals by activated neutrophils, protects vascular endothelial cells from neutrophil-mediated injury, and inhibits the adherence and activation of neutrophils at sites of inflammatory injury. In this study, exogenous adenosine reduced tissue myeloperoxidase concentration compared with untreated tissue (Figure 2). Since tissue myeloperoxidase concentration is a reliable index of neutrophil infiltration in the ischemic intestine, these results suggest that the protective mechanism of adenosine might involve inhibition of neutrophil function and O2 radical generation. In addition, these results support the hypothesis that endogenous adenosine links the catabolism of ATP to neutrophil inhibition.

Nevertheless, it is unlikely that inhibition of neutrophil function was the sole mechanism by which adenosine attenuated intestinal reperfusion injury because prostacyclin did not have a similar effect. Previous studies have shown that prostacyclin protects reperfused myocardium, and this effect has been attributed to inhibition of neutrophil migration. In these present experiments, a continuous suffusion with a PGI2 solution that was equally effective with adenosine for causing vasodilation was not equally effective for protecting the reperfused tissue. However, it must be emphasized that the efficacy of PGI2 at higher doses or the efficacy of adenosine at lower doses was not tested.

Intracoronary adenosine attenuated coronary reperfusion injury by attenuating the no-reflow phenomenon. We observed that topical adenosine produced a similar effect in the intestine (Tables 1 and 2, Figure 1). However, it is unlikely that vaso-

References


KEY WORDS • prostacyclin • acetylcholine • granulocyte • jejunum
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