Possible Role for Adenosine in Local Regulation of Absorptive Hyperemia in Rat Intestine

Kenneth G. Proctor

To test whether extracellular adenosine participates in the local regulation of intestinal blood flow during nutrient absorption, the serosa of the jejunum was continuously suffused with adenosine deaminase (7 μg protein/ml) or theophylline (10^{-4} M) in Ringer's solution. Using video microscopy, blood flow was calculated in submucosal arterioles from diameter and red cell velocity measurements. 

After a steady-state baseline, oleic acid (20 mM) + glucose (56 mM) were added to a bile salt solution suffusing the mucosa. Baseline arteriolar diameters and blood flows were 52 ± 2 μm and 20 ± 2 nl/sec with the serosal suffusate containing Ringer's; these values were not significantly altered by theophylline or deaminase treatment. During suffusion of the mucosa with a nutrient solution, diameter and blood flow transiently increased and these responses were not altered by deaminase or theophylline. Thereafter, diameter and blood flow stabilized at lower values for the duration of absorption. Diameter and blood flow were increased to 111 ± 1% and 134 ± 5% of control during absorption with Ringer's; the corresponding values were significantly lower with deaminase or theophylline. After absorption, diameter and blood flow stabilized near baseline with Ringer's within 7–12 minutes; the corresponding values were significantly lower with deaminase or theophylline for at least 30 minutes.

Since deaminase and theophylline produced similar effects on absorptive hyperemia, adenosine might participate with other factors in the local regulation of that response. Adenosine applied to the serosa caused dose-dependent increases in calculated blood flow with a threshold near 10^{-5} M and a maximum near 10^{-3} M. In contrast, even 10^{-2} M adenosine in the mucosal suffusate did not increase blood flow above baseline. Until the mechanism for this regional difference between the mucosa and serosa is defined, it will be difficult to localize the site of action of adenosine within the intestinal wall or estimate its concentration in the perivascular space of intestinal arterioles. (Circulation Research 1986; 59:474–481)

INTESTINAL blood flow is regulated by a complex interaction between systemic neurogenic influences, circulating vasoactive substances, and local factors. During absorption, local factors are particularly important because functional hyperemia occurs even in isolated gut loops. Some evidence suggests that adenosine is a component in the local regulatory mechanism.

The purpose of this study was to test the hypothesis that adenosine mediates local intestinal blood flow changes during absorption. A microcirculatory approach was used, and the role of adenosine was indirectly estimated by reducing its vasoactive expression in the extracellular space with adenosine deaminase or theophylline. Adenosine deaminase catalyzes the conversion of adenosine to inosine, which is a less potent vasodilator. Theophylline competitively antagonizes adenosine receptors. If absorptive hyperemia is mediated by adenosine, then adenosine deaminase and theophylline should attenuate the response.

Methods

Male Sprague-Dawley rats (120–250 g) were anesthetized with 13% urethane and 1% chloralose (1.2 ml/100 g i.p.). Supplemental doses were administered when necessary (0.1 ml/100 g i.v.). The trachea, carotid artery, and jugular vein were cannulated. Respiration was spontaneous on room air. Rectal temperature was continuously monitored (YSI) and maintained at 36–38°C with a heat lamp. Arterial blood PO_2, PCO_2, and pH were periodically measured on a Radiometer analyzer and were typically >70 mm Hg, <40 mm Hg, and 7.40–7.45, respectively, in these conditions. Carotid arterial blood pressure was continuously monitored with a Gould-Statham P23ID transducer and typically ranged between 80 and 100 mm Hg.

The intestine was prepared with a slight modification of a technique developed by Bohlen and Gore. Briefly, an incision along the antimesenteric border of the jejunum was heat cauterized. Several ties were sutured to the two flaps of tissue. The upper flap was retracted. The lower flap was gently pulled to a flattened sheet over a glass viewing port on a specially designed animal board. A chamber top was lowered onto the preparation so that the tissue was completely enclosed in a controlled environment.

The mucosal (upward-facing) and serosal (downward-facing) surfaces were each suffused with bicarbonate-buffered Ringer's solutions comprised of (mM) NaCl 131.9, KCl 4.7, CaCl_2 2.0, MgSO_4·H_2O 1.2, and NaHCO_3 20. Ascorbic acid (0.5 mM) was added as an anti-oxidant. Solution gas tensions and pH were maintained by vigorous bubbling with a gaseous mixture of 5% CO_2, 5% O_2, and 90% N_2 in glass chambers encased in water jackets at 37°C. The glass chambers were connected to the mucosal and serosal perfusion
chambers of the animal board by thick-walled rubber tubing. Tissue temperature was continuously monitored (YSI LN 3207) and maintained at 36–37°C by varying the flow rates of the heated solutions that suffused the mucosa (average = 3–7 ml/min) and serosa (average = 1–3 ml/min). Isoproterenol (Sigma) was added to the serosal suffusate to suppress spontaneous intestinal motility. The threshold concentration for increasing calculated intestinal blood flow was 1 μM, which is 25× higher than the maximum concentration used in these studies. In 10–25% of the preparations, motility could not be suppressed because of improper anesthetic level, mixing of mucosal and serosal suffusates, surgical damage, or excessive tension on the tissue. If motility could not be suppressed, the experiment was terminated, since accurate measurements were impossible.

The microcirculation was transilluminated with white light from a stable DC power supply (Stahl model 576). Observations were made with long-working-distance (4–6 mm) objectives (Leitz L20 × , 0.32 numerical aperture or L32 × , 0.40 numerical aperture), a long-working-distance condensor (Leitz L-11, 0.60 numerical aperture), and a Leitz Diavert microscope equipped with a trinocular head and discussion bridge (Leitz #24875-512). The optics were aligned in accordance with Kohler’s principle to remove the contrast-reducing flare of scattered light from outside the visual field. The discussion bridge provided coincident images to a color television camera (Panasonic #3230, newvicon tube) and a rotating prism velocitometer. The television signal was conveyed to a video micrometer (For-A IV-550) and high-resolution color monitor (Panasonic CT 1930V). The video micrometer generated two moveable parallel lines on the monitor that were positioned on the inner aspects of the arteriolar walls. The distance between the lines were converted to an analog voltage that was continuously measured. The line separation was calibrated with a stage micrometer to ±1 μm.

The rotating prism velocimeter was custom-designed (Micro-Precision) for the purpose of measuring red blood cell velocity. The mechanical image-streaking principle that served as a basis for a similar instrument was previously described. The rotating prism method favorably compares with the more conventional dual-slit photometric method for measuring red blood cell velocity in the microcirculation.

**Experimental Protocol**

After a 30- to 60-minute postsurgery stabilization period, a first-order arteriole in the submucosal microcirculation (resting diameter 40–70 μm) was tested for the presence of spontaneous vasomotor tone by the continuous topical application of adenosine (Sigma: 10⁻⁴ – 10⁻³ M) to the serosa. The typical response was a steady-state increase in diameter and calculated blood flow. Experiments were terminated if motility was excessive, if a preparation lacked vasomotor tone, if the adenosine-induced response was not reversible, or if systemic arterial blood pressure decreased below 70 mm Hg. Considering all factors, more than 50% of the experiments were terminated. At the end of a successful experiment, 10⁻² M adenosine was applied to the serosa to obtain a steady-state maximum blood flow and diameter.

Arterial blood pressure, arteriolar diameter, red cell velocity, and tissue temperature were continuously recorded on a Gould polygraph. The hemodynamic variables were digitized every 5 seconds by a Commodore microcomputer. Blood flow was computed on-line from the product of a constant, arteriolar diameter, and red blood cell velocity and recorded on a DECwriter. Each hemodynamic variable was averaged over a 30- to 60-second interval every 2–6 minutes.

The mucosa was suffused in sequence with a bile salt solution for 10–30 minutes, nutrient solution for 10 minutes, then bile solution for 30 minutes. Bile salt emulsified the lipid; the solution consisted of 10 mM taurocholic acid (Sigma) in bicarbonate-buffered Ringer’s. The nutrient solution consisted of 20 mM oleic acid (Sigma) + 56 mM glucose (Fisher) in bile salt solution. Solution osmolality was measured by freezing point depression (Precision Systems) and averaged 340 ± 2 mOsm/kg for the nutrient solution, 318 ± 1 mOsm/kg for the bile salt solution, and 293 ± 2 mOsm/kg for bicarbonate-buffered Ringer’s only. Solution pH was measured on a Radiometer analyzer and averaged 6.86 ± 0.06 for the nutrient solution, 7.43 ± 0.02 for the bile salt solution, and 7.35–7.45 for bicarbonate-buffered Ringer’s only.

Adenosine deaminase was dialyzed for 24 hours to remove small-molecular-weight contaminants and frozen in 5-ml aliquots in bicarbonate-buffered Ringer’s (72 μg protein/ml) until the day of the experiment. The dialysis procedure was described in detail in our previous work. Individual aliquots were thawed and added to the serosal suffusate to a final concentration of 7 μg protein/ml suffusate. Enzyme activity was measured in vitro in samples that had previously been dialyzed, frozen, and thawed. These data are presented in “Results.”

The serosal suffusate contained either a bicarbonate-buffered Ringer’s vehicle, vehicle + adenosine deaminase (Sigma type III, 1100 U/mg protein), or vehicle + theophylline (Sigma). After deaminase or theophylline were added to the serosal suffusate, approximately 20 minutes was allowed for the substances to equilibrate with the tissue.

The sequence of vehicle–deaminase and vehicle–theophylline applications was randomized. If a preparation remained viable, paired responses with vehicle and either deaminase or theophylline were collected in individual animals. Between each response, at least 30–60 minutes was allowed for washout and to reestablish a steady-state baseline. Thus, each deaminase and theophylline response was paired with its own steady-state baseline, and most responses were paired with a steady-state vehicle baseline.

The dose of deaminase was based on the theoretical
calculations previously described. The dose of theophylline was based on empirical observation. Adenosine ($10^{-4}$ M) was continuously applied to the serosa to produce steady-state hyperemia. Ascending amounts of theophylline were added to the serosal suffusate until the steady-state hyperemia was attenuated. The effectiveness of $<10^{-4}$ M theophylline varied between individual preparations, but $10^{-4}$ M theophylline attenuated adenosine-induced hyperemia in all animals. These data are presented in "Results." In a few animals, $10^{-4}$ M theophylline produced irreversible vasodilation, so these animals were excluded from the study population.

Statistical Analysis

All values were expressed as means ± SE. Most comparisons were paired and all treatments were randomized. Differences were determined with paired or unpaired t tests. Significance was assessed at the 95% confidence interval.

**Results**

**Effect of Adenosine Deaminase or Theophylline on Absorptive Hyperemia**

Neither substance altered baseline hemodynamic variables, but both reduced the microcirculatory response to nutrient absorption.

Systemic arterial blood pressure, intestinal arteriolar diameter, and calculated arteriolar blood flow are shown in animals treated with both vehicle and deaminase and in animals treated with both vehicle and theophylline (Table 1). None of the apparent differences were statistically significant. Theophylline caused vasodilation in 4 out of 5 animals; but the overall change was not significant, and calculated blood flow values were comparable between the vehicle and theophylline treatments. Perhaps a significant effect of theophylline would have become evident in a larger sample. On the other hand, it is equally possible that the apparent vasodilation caused by theophylline was a nonspecific side effect because deaminase tended to change arteriolar diameter in the opposite direction.

After deaminase or theophylline was added to the TABLE 1. Effect of the Local Application of Adenosine Deaminase or Theophylline on Hemodynamic Variables in Resting Steady-State Conditions

<table>
<thead>
<tr>
<th></th>
<th>n (animals)</th>
<th>Arterial blood pressure (mm Hg)</th>
<th>Arteriolar diameter (μm)</th>
<th>Calculated blood flow (nl/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>vehicle</td>
<td>10</td>
<td>90 ± 2</td>
<td>57 ± 4</td>
<td>24 ± 3</td>
</tr>
<tr>
<td>ADA</td>
<td>9 ± 3</td>
<td>91 ± 4</td>
<td>53 ± 4</td>
<td>25 ± 3</td>
</tr>
<tr>
<td>vehicle</td>
<td>5</td>
<td>87 ± 3</td>
<td>51 ± 3</td>
<td>23 ± 4</td>
</tr>
<tr>
<td>THEO</td>
<td>82 ± 2</td>
<td>57 ± 1</td>
<td>22 ± 1</td>
<td></td>
</tr>
</tbody>
</table>

All values are mean ± SE. ADA (adenosine deaminase) concentration in serosal suffusate was 7 μg/ml. THEO (theophylline) concentration in serosal suffusate was $10^{-4}$ M. The sequence of vehicle, ADA, and THEO treatments was randomized. There were no significant differences.

serosal suffusate, systemic blood pressure and arteriolar diameter remained near the control values measured with the vehicle only (Figure 1). Calculated blood flow was significantly decreased at two time increments after deaminase, but the fluctuation was transient: After 20 minutes of treatment, all variables were virtually indistinguishable from the pretreatment baseline.
significant peak values were observed at various times during absorption. Systemic arterial blood pressure remained near baseline after absorption, but calculated transient peak values were observed at various times during absorption in individual animals. Diameter remained near baseline after absorption, but calculated blood flow was significantly decreased below baseline for 7–30 minutes after absorption.

In 5 animals treated with theophylline for 22 ± 3 minutes, calculated blood flow averaged 22 ± 1 nl/sec at a diameter of 57 ± 1 μm during baseline conditions. Neither value was significantly elevated during absorption with theophylline treatment. The lack of absorptive hyperemia during theophylline treatment was similar to the effect of deaminase on the response. After absorption, diameter and calculated blood flow tended to decrease below baseline, but these apparent differences were not significant. The similar effects of deaminase and theophylline suggest that adenosine may be a factor regulating intestinal blood flow during and following absorption.

The data in Figure 3 show the peak hemodynamic variables during absorption. In individual animals in each group, the addition of nutrients to the mucosal suffusate caused initial increases in calculated blood flow and diameter, which subsequently decreased to lower steady-state values for the duration of the absorptive period. Since the time of occurrence varied for these brief transients, the effect was not manifest in Figure 2. The peaks in diameter and blood flow in all three groups were significantly elevated above baseline and not different between groups. Since a response persisted in the presence of deaminase or theophylline, these data suggest that adenosine is not the only factor regulating absorptive hyperemia.

The pooled responses for calculated blood flow and diameter during the entire absorption period are shown in Figure 4. Blood flow was significantly elevated to 134 ± 5% with vehicle treatment. The values with deaminase (105 ± 5%) or theophylline (109 ± 5%) were not different than the baseline and both were significantly less than paired vehicle responses. Diameter was significantly increased during absorption with both vehicle and deaminase, but not with theophylline. The paired difference between vehicle and theophylline was significant.

The pooled responses after absorption are shown in Figure 5. Both diameter and blood flow were virtually identical to the pre-absorption baseline over this 30-minute interval if the serosal suffusate contained the Ringer's vehicle only. In the deaminase-treated group, average blood flow was significantly below baseline and significantly less than paired vehicle responses. In the theophylline-treated group, blood flow tended to decrease below baseline, but the difference was not significant. However, diameter with theophylline was significantly below the baseline and significantly less than paired vehicle responses.

Efficacy of Adenosine Deaminase and Theophylline

The reaction velocity of adenosine deaminase was measured in vitro at 25°C by observing the change in absorbance as adenosine was deaminated. This procedure was modified from that described by Agarwal et al.12 In bicarbonate-buffered Ringer's at pH 7.4 and an initial adenosine concentration of 1 mmol/ml, 0.07 μg enzyme/ml converted 0.83 mmol adenosine/ml to inosine in the first minute. The reaction was 97% complete after 2 minutes. These data indicate that deaminase activity was not seriously altered by diluting the original enzyme solution with bicarbonate-buffered Ringer's and then dialyzing, freezing, and thawing the
Ringer's enzyme solution. These data do not provide any information on adenosine deaminase activity in vivo.

The steady-state hyperemia induced by adenosine was significantly reduced by $10^{-4}$ M theophylline, as shown in Figure 6. With $10^{-4}$ M theophylline in the serosal suffusate, $0.54 \pm 0.11$ mM adenosine elicited a diameter increase to $115 \pm 5\%$ of control and a hyperemia that averaged $166 \pm 20\%$ of control in 10 animals. Both of these values were significantly elevated above the baseline. However, with no theophylline in the suffusate, a smaller dose of adenosine ($0.50$ mM) elicited a bigger response: Diameter increased to $151 \pm 9\%$ of control, and blood flow increased to $303 \pm 29\%$ of control in 14 animals. Both of these values with vehicle were significantly greater than the values with theophylline, which demonstrates that endogenous adenosine receptors were antagonized in these experimental conditions.

**Figure 3.** Peak diameter (top, left) and peak calculated arteriolar blood flow (bottom, left) in individual animals during absorption. * = significant difference from paired baseline. Since the time to reach these transient values varied in each animal, this effect was not seen when diameter and BFC were plotted against time in Figure 2. Some absorption responses were repeated twice in the same animal with the treatments applied in random order. These paired differences in peak diameter (top, right) and peak blood flow (bottom, right) were not significant.

**Adenosine Dose-Response**

Steady-state blood flow and diameter changes as a function of mucosal or serosa adenosine concentration are shown in Figure 6. Adenosine in the serosal suffusate caused a dose-related increase in submucosal blood flow and diameter with a threshold near $10^{-3}$ M. At $2.5 \times 10^{-4}$ M adenosine, diameter had reached its maximum near $150\%$ of control. Calculated blood flow continued to increase until a maximum was reached near $400\%$ of control at $10^{-3}$ M. Since diameter had peaked but blood flow continued to increase, downstream dilation must have occurred, at least with adenosine doses greater than $2.5 \times 10^{-4}$ M.

There was no observable effect of mucosal adenosine over the concentration range of $10^{-5} - 10^{-2}$ M. With $10^{-3}$ M adenosine in the mucosal suffusate, blood flow averaged $167 \pm 32\%$ of control and diameter averaged $106 \pm 15\%$ of control in 4 animals. Neither of these values were significantly elevated above base-
Adenosine and Intestinal Hyperemia

AVERAGE VALUES POST OA+GLU

![Graph showing average values post OA+GLU](image)

**FIGURE 5.** Average diameter (top, left) and average calculated blood flow (bottom, left) during the 30-minute after absorption period in the 3 treatment groups. * = significant difference from paired baseline. For those treatments repeated twice in the same animal, * = significant difference between vehicle and drug.

Discussion

This study showed that adenosine deaminase or theophylline reduced (Figures 2, 4, and 5), but did not eliminate (Figures 2 and 3), the intestinal vasodilation elicited by nutrient absorption without altering hemodynamics in the nonabsorbing tissue (Table 1, Figure 1). These data support the concepts that resting intestinal blood flow is not mediated by adenosine and that adenosine is one of, perhaps, several mediators of intestinal functional hyperemia.

Critique

The major limitation of this study is that tissue adenosine was not actually measured. It is reasonable to conclude that adenosine is a mediator of intestinal absorptive hyperemia because the response was reduced by both adenosine deaminase and theophylline, which are structurally dissimilar compounds with different mechanisms of action. However, the validity of this conclusion depends on the assumption that the vasoactive expression of adenosine was inhibited by these compounds. Adenosine deaminase is relatively specific, but its action might have been limited by restricted access to the site of adenosine's action and its relatively low affinity for the adenosine molecule compared to the vascular smooth muscle receptor. In contrast, the efficacy of theophylline would not be compromised by diffusive access and its receptor affinity is high; but its utility is limited by nonspecific side effects.

Both deaminase and theophylline probably had access to the perivascular space because of the demonstrable effects on absorptive hyperemia (Figures 2, 4,
and 5). In this study, nutrients were added to the mucosal suffusate approximately 20 minutes after deaminase or theophylline were added to the serosal suffusate. In a previous study, we calculated that at least 10 minutes was required for the concentration of deaminase in the tissue extracellular space to reach 90% of the concentration in a suffusate. This calculation was based on the assumptions that the free diffusion coefficient of deaminase was no greater than that of albumin, that the size of the enzyme was 32,000–35,000, and that the tissue thickness was 200–500 μm. Reference to this publication cannot support the contention that deaminase reached a steady-state tissue concentration within 20 minutes or that the concentration within the tissue was adequate to completely block the vasoactive expression of endogenous adenosine.

Because deaminase and theophylline were applied only to the serosal surface, it is possible that there was a regional difference in the vasoactive expression of adenosine within the intestinal wall. Deaminase was not added to the mucosal suffusate because proteins in a mucosal suffusate can elicit absorptive hyperpermia. If deaminase had produced metabolic hyperpermia by virtue of its protein nature, then its effect on endogenous adenosine vasoactivity would have been masked. Although theophylline would not have elicited a protein-induced hyperpermia, it would have been difficult to directly compare results obtained with deaminase if the two substances were not administered by the same route.

The suffusate concentration of deaminase was excessive compared to the maximum tissue adenosine production rate to assure that vasoactive effect of endogenous adenosine was reduced. In our earlier work, we calculated that even if the deaminase concentration within the tissue extracellular space had been 90% lower than the sulfusate concentration and even if the entire adenosine production capacity of the tissue had been localized in only 2% of the available tissue volume, the rate of deamination would have exceeded the maximum theoretical rate of adenosine production by more than threefold. Nevertheless, these calculations must be considered highly speculative because the activity of the enzyme in vivo may differ from that measured in vitro. Therefore, it can only be assumed that the perivascular deaminase concentration was adequate to block the vasoactive expression of adenosine. Furthermore, because of the kinetics of the enzymatic reaction, it cannot be assumed that deaminase blocked the expression of a continuous low-level production of adenosine or that deaminase blocked the expression of brief bursts of adenosine release.

Theophylline might have produced nonspecific alterations on the intestinal microcirculation at the dose (10^4 M) required to attenuate adenosine-induced hyperpermia. However, neither baseline blood flow nor diameter (Table 1) were significantly altered and the effect of theophylline on intestinal hemodynamics was comparable to the effect of deaminase (Figures 1–5). The drug might have distorted some other aspect of tissue function (e.g., phosphodiesterase activity) that was not measured, but within the limits of experimental error, we detected no nonspecific effect of theophylline.

It is important to emphasize that blood flow was calculated in this study and not actually measured. We previously reported that microcirculatory blood flow calculations are not necessarily accurate or proportional to total tissue blood flow. However, the glucose-induced blood flow change in this preparation agrees with results that other investigators have observed with different experimental designs in the rat, dog, and cat. This correlation between macro- and microcirculatory variables during intestinal hyperemia lends credence to the critical assumption of this study that calculated arteriolar blood flow changes are representative of total tissue blood flow changes.

**Interpretation**

Berne outlined several criteria for a metabolic mediator of blood flow, one of which is that "the physiological effect at different concentrations of the endogenous mediator should be mimicked by exogenous administration of the substance". In this present study, exogenous adenosine applied to the serosa caused a dose-dependent increase in calculated submucosal blood flow with a threshold near 10^-3 M and a steady-state maximum near 10^-2 M (Figure 6). Although these adenosine concentrations are supraphysiologic, these data neither support nor deny a role for adenosine as a vasoregulator. Adenosine has direct receptor effects that cause blood flow increases, but metabolic effects in the intestine (i.e., decreased oxygen consumption) that cause blood flow decreases. Indeed, because of complicated interactions between its direct and indirect effects, Daly stated that "adenosine might profitably be omitted from any list of nucleosides to be used for characterization of adenosine-mediated responses." To separate the direct vascular actions of adenosine from the metabolic effects, it will be necessary to use synthetic analogues that are receptor agonists but not metabolic substrates.

Daly's message is underscored by the fact that mucosal adenosine produced no increase in submucosal blood flow, even at 10 × the maximal serosal dose (Figure 6). Similar findings have been reported by Shepherd et al and Granger et al, who both observed reductions in mucosal blood flow with an arterial infusion of adenosine. Granger et al attributed the effect to mucosal vasoconstriction whereas Shepherd et al attributed the effect to a vascular steal phenomena.

It is conceivable that adenosine in the mucosal suffusate never reached the submucosal arteriole where blood flow was calculated. Perhaps the intestinal epithelial cells incorporated adenosine into their intracellular nucleoside pool. Perhaps the mucosal surface restricted the diffusion of adenosine into the submucosal interstitium. Perhaps adenosine caused a decrease in mucosal oxygen consumption, which masked an increase in serosal blood flow. Alternatively, perhaps there is a regional difference in the distribution of
Adenosine receptors between the intestinal serosa and mucosa. In any case, the mechanism of the regional difference in the adenosine response is not known and further study is warranted.

Other investigators have postulated a role for adenosine in intestinal vasoregulation. The biosynthetic pathways have been well-described; intestinal blood vessels respond to exogenous adenosine with dose-dependent responses; vascular receptors are sensitive to adenosine concentrations in the physiologic range; and drugs that interfere with the metabolism of adenosine produce directional changes in blood flow consistent with the adenosine hypothesis. The results of this study further support an earlier hypothesis that the importance of adenosine for intestinal blood flow control is proportional to metabolic demand.

Actively absorbed glucose acts primarily on exchange vessels in the intestinal wall to increase oxygen extraction from the blood, while passively absorbed oleic acid primarily acts on resistance vessels to increase oxygen delivery to tissue. The results of this study suggest that extracellular adenosine may be one of the factors that mediates the hyperemia that accompanies absorption of oleic acid + glucose. A possible role of adenosine in the regulation of intestinal blood flow should be considered in the context of our two recent studies that suggest that nonprostaglandin metabolites of arachidonic acid might also contribute to the regulation of intestinal blood flow during oleic acid absorption. The absorption of oleic acid also triggers the release of histamine and other vasoactive intestinal hormones. Thus, the relative contribution of the various mediators to the local control of intestinal blood flow probably depends on the composition of the meal and on the intestinal metabolic rate.

Acknowledgments

The author gratefully acknowledges the expert assistance of M. Katherine Klyce and Mary Elizabeth Hayes.

References


Key Words • adenosine deaminase • theophylline • blood flow
Possible role for adenosine in local regulation of absorptive hyperemia in rat intestine.

K G Proctor

Circ Res. 1986;59:474-481
doi: 10.1161/01.RES.59.4.474

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1986 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/59/4/474