

## Review article

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E. D. JACOBSON, W. W. PAWLIK

### ADENOSINE MEDIATION OF MESENTERIC BLOOD FLOW

Departments of Medicine and Physiology, University of Colorado School of Medicine, Denver,  
Colorado, U. S. A.

Institute of Physiology Academy of Medicine Krakow, Poland

The mesenteric circulation is regulated by multiple mechanisms, there is sufficient reason to support the suspicion that local metabolic factors are especially important in the control of intestinal vasculature. Of these, adenosine, a purine nucleoside and mesenteric vasodilator, may be the messenger of the intestinal tissue to signal appropriate responses of the intestinal vessels. The evidence supporting the candidacy of the nucleoside as a local regulator of mesenteric circulation may be summarized, as follows: Adenosine is present in the tissue of the gut in measurable quantities. Exogenous adenosine is a powerful dilator of mesenteric resistance vessels. Blockade of adenosine receptors in the mesenteric circulation interferes significantly with three autoregulatory phenomena, i. e., postprandial hyperemia, pressure-flow autoregulation, and reactive hyperemia. The evidence which weakens the role of adenosine as mesenteric vasoregulator includes: Findings in several reports that adenosine depressed intestinal oxygen consumption. The failure of adenosine receptors to inhibit some autoregulatory hyperemias of the gut and the rather limited amount of evidence regarding tissue adenosine release in autoregulatory responses of the gut's vasculature.

**Key Words:** *adenosine receptors, intestinal circulation, intestinal autoregulatory hyperemias.*

#### GENERAL CONSIDERATIONS

Joseph Barcroft may have originated the time-honored concept that the altered chemical environment produced by tissue metabolism relaxes nearby vascular smooth muscle to elicit an increase in local blood flow (1). Although

the mesenteric circulation is regulated by multiple mechanisms, there is sufficient reason to support the suspicion that local metabolic factors are especially important in the control of blood flow through the intestinal vasculature (2). Among other considerations, the superior mesenteric artery has been found to exhibit a variety of discrete autoregulatory responses, in which the challenge of either a diminished blood flow or an increased oxygen demand is met by a localized hyperemia of the gut. Examples of such intestinal autoregulatory phenomena include postprandial hyperemia (3), pressure-flow autoregulation (4), reactive hyperemia (5), autoregulatory escape (6), and post stimulation hyperemia (7). While the mediation of locally controlled, enteric hyperemias is likely to involve numerous paracrine and neurocrine substances, as well as vasodilator metabolites, nearly all research in this area has tended to focus narrowly on single mediator candidates, without much consideration of complementary systems.

The 3 major requirements for validating such putative mediators of locally regulated mesenteric hyperemias are: 1) the substance must be present in intestinal tissue in measurable amounts, which increase with either a reduced blood supply or an enhanced parenchymal metabolism; 2) the agent must be a potent relaxant of mucosal resistance vessels and must increase blood flow through mucosal, nutrient capillaries; and 3) the proposed mediator should have effective antagonists of either its synthesis or its vascular receptor binding, as well as effective pharmacological stimulants, which raise its local concentration, and should have been shown to fulfill the role of vasodilator metabolite in at least one other peripheral circulation (8, 9). Several types of intestinal vasodilator chemicals have been investigated, with the foregoing criteria in mind, such as eicosanoids, peptides, amines, and purines (2). Among these, the single substance which has been most thoroughly studied and which best meets the foregoing standards of a dilator metabolite in the mesenteric circulation is the ribonucleoside, adenosine. This review will explore the possible physiological roles of this purine metabolite in the intestinal vasculature.

#### EFFECTS OF ADENOSINE ON THE MESENTERIC CIRCULATION

Abundant evidence supports the designation of adenosine as a mesenteric vasodilator agent. The usual way to demonstrate this property of the nucleoside is to infuse adenosine directly into the superior mesenteric artery or one of its main branches. Doses of adenosine, which do not alter systemic arterial blood pressure but do increase blood flow and vascular conductance, are considered to have passed the test of a vasodilator agent in this circulation (10). However, even in such "constant pressure" preparations, we lack a critical piece of evidence. There is no proof that adenosine concentrations are comparable at

purinergic, vascular receptor sites in 2 different situations: a) the hyperemia evoked by spontaneous release of endogenous adenosine in response to a physiological challenge, e. g., feeding; and b) an equivalent hyperemia produced by intraarterial infusion of exogenous adenosine.

Vasodilator effects of adenosine have been demonstrated during *in vivo* experiments in dog (8, 9, 11—19), cat (10, 20—24), rat (25—29), rabbit (25), and pig (30) gut, in which intestinal blood flow was ascertained with various techniques. Furthermore, the threshold dose of exogenous adenosine, which increased mesenteric blood flow significantly, was in the micromolar range (9). This dose approximates the amount of endogenous adenosine measured in mesenteric venous blood during postprandial hyperemia (31) or reactive hyperemia (32). In addition, a synthetic analogue of adenosine, 2-chloroadenosine, also dilated the mesenteric circulation (17, 28, 33), and both substances relaxed KCl-contracted strips of mesenteric artery under *in vitro* conditions (17, 34, 35).

The effect of exogenous adenosine on intestinal oxygen consumption is more problematic, and its investigation has produced conflicting results, which, however, do not necessarily negate the role of the nucleoside as a dilator metabolite. Thus, it was found that adenosine and 2-chloroadenosine increased oxygen uptake, total blood flow, the density of perfused capillaries, and the distribution of blood flow to the mucosal and submucosal layers of the gut wall (17, 33). These findings support the concept that adenosine vasodilation favors perfusion of metabolically active tissue, especially in the intestinal mucosa, in which site blood flow and oxygen availability would be rate-limiting steps for enhancing local metabolism (36). However, other laboratories have reported that exogenously administered adenosine reduced oxygen consumption, PS-product, and the capillary filtration coefficient, despite either vasodilating the mesenteric circulation in constant flow preparations or increasing blood flow in constant pressure preparations (8, 9, 12, 15, 21, 37). Adenosine was even reported to decrease oxygen uptake of *in vitro* mucosal and muscularis strips (21). The explanation offered for the antimetabolic effect of adenosine in resting gut *in vivo* was a "vascular steal" phenomenon, i. e., a redistribution of blood flow away from the metabolically more active mucosa into the quiescent muscularis of the intestinal wall (12, 15, 21). These findings are not readily reconciled with the proposed role of adenosine as a mediator of postprandial hyperemia, for example. As will be apparent in Section III of this review, there is agreement among a plethora of reports that the instillation of nutrients into the gut increases not only blood flow but also oxygen consumption, and enhances the distribution of blood flow into the nutrient circulation of the mucosa.

The case for adenosine as a dilator metabolite has been bolstered by observing mesenteric circulatory responses to drugs, which either prevent or antagonize vascular effects of exogenously administered adenosine, and to

agents, which augment effects of this nucleoside in the circulation. The older receptor antagonists, theophylline and aminophylline, exhibited inhibitory properties at both of the adenosine receptor sites and significantly reduced mesenteric vasodilator responses either to adenosine (17, 19, 21) or to proposed, adenosine-mediated, locally regulated hyperemias of the gut (8, 9, 11, 22, 38—41). The more potent adenosine antagonist, 8-phenyl theophylline, has also been found either to inhibit circulatory responses to adenosine in the gut (10, 22, 23, 29, 42) or to interfere with autoregulatory hyperemias, in which adenosine is presumed to be the dilator metabolite (11, 20, 22, 23, 29, 40). The enzyme, adenosine deaminase, converts adenosine into the much weaker metabolite, inosine. Parenteral administration of adenosine deaminase either inhibited the dilator response to adenosine (29) or suppressed autoregulatory hyperemias, supposedly mediated by the nucleoside (29, 38, 39). Furthermore, adenosine deaminase has been found to reduce cardiac, interstitial adenosine content (43), whereas inhibition of the enzyme in the ileum enhanced the stimulatory effects of exogenously administered adenosine on adenylate cyclase and on  $\text{Cl}^-$  transport (44). Dipyridamole interferes with cellular uptake of endogenously released adenosine, thereby effectively maintaining or increasing local concentrations of the nucleoside (45). Dipyridamole possesses the properties of an intestinal vasodilator agent and augments the mesenteric vasodilation elicited by adenosine (9, 13, 18, 19). The vasodilator effects of adenosine appear to be mediated by binding of the nucleoside to the adenosine  $A_2$  receptor site on either vascular smooth muscle or endothelium (13, 28, 46).

Additional actions of adenosine in the gut, which would be expected to contribute to mesenteric vasodilation include: 1) inhibition of the release of norepinephrine from postganglionic, vasomotor nerves (47, 48) — although this effect has been disputed (49, 50) — as well as antagonism of the constrictor response of isolated mesenteric arteries to norepinephrine (34); 2) enhancement of the release of acetylcholine from parasympathetic nerves to the gut (51); 3) augmentation of intestinal active secretion of  $\text{Cl}^-$ , with, presumably, an increase in mucosal metabolism (44, 52); and 4) increase in the mucosal content of adenine nucleotides (44, 46, 52), which have been shown to be mesenteric vasodilator agents, such as cyclic AMP (16, 52, 53) and ATP (16, 19, 54—57). Conversely, the intestinal tissue content of adenine nucleotides is reduced during mesenteric ischemia and shock states (58—60), and adenosine protects the gut against ischemic damage (13, 14, 26, 42, 61).

The hepatic circulation bears both an in-series relationship (mesenteric veins are branches of the portal vein) and a parallel relationship (mesenteric arteries and the hepatic artery are first order branches of the abdominal aorta) to the circulation of the gut. There appears to be a role for adenosine in autoregulatory events in the liver (62). Adenosine receptors have been confirmed in the hepatic artery but not in the portal vein (63). Pressure-flow

autoregulation in the hepatic artery was inhibited by either of 2 receptor antagonists of adenosine (64). When portal venous flow was grossly reduced by partial or complete occlusion of the vessel, there was an increase in blood flow through the hepatic artery, which partly compensated the liver for the portal ischemia (65). This hepatic arterial hyperemia is believed to be autoregulatory and is also inhibited by adenosine receptor antagonists (64, 66, 67). Direct infusion of adenosine into the hepatic artery prompted a vasodilator effect (65), whereas systemic administration of the nucleoside in doses which produced significant hypotension, nevertheless increased portal venous blood flow, while reducing hepatic arterial perfusion (18). It has been proposed that accumulation of the nucleoside results from a reduction in the washout of adenosine from the liver by the portal circulation, and that the local increase in adenosine content vasodilates the hepatic artery (64, 66). Direct infusion of the nucleoside into the portal vein also dilates the hepatic artery (66, 68), and this effect is impaired by adenosine receptor antagonists (67, 69). Some of the vasodilator response to adenosine in the liver is antagonized by caffeine (24).

Consumption of ethanol presents numerous stresses to the human liver, and adenosine appears to mediate some of the hepatic circulatory effects of ethanol. The second metabolite of ethanol in the liver is acetate, which circulates to preportal viscera, such as the gut, where it is converted to acetyl CoA (70). This reaction is driven by the hydrolysis of ATP, which yields adenosine. The latter nucleoside binds to its  $A_2$  receptor in the mesenteric circulation, thereby dilating the resistance vessels of the gut and augmenting the flow of blood into the portal vein. In addition to the enhancement of vascular perfusion through the portal tributaries, there is a hyperemia in the hepatic artery (71). Instillation of ethanol in the lumen of the gut elicits an increase in intestinal blood flow comparable to postprandial hyperemia (72). The ability of either ethanol or acetate to evoke release of adenosine from the gut and the liver into the blood does not appear to be secondary to local ischemia or stimulation of metabolism in the digestive organs (72). The preportal, portal, and hepatic arterial hyperemias evoked by either ethanol or acetate were suppressed by 8-phenyl theophylline (70, 71, 73). Furthermore, administration of ethanol by gavage in rats prompted a large increase in circulating concentrations of adenosine (73). It should be noted that the vasodilator effect of acetate in exercising, voluntary muscle also appears to be mediated by local release of adenosine (74).

There is, of course, an extensive literature, which delineates the role of adenosine as a local regulator of vascular perfusion in other regional circulations (75). A recent review documents numerous reports, which identify adenosine as the dilator metabolite in the circulations of the heart, brain, and voluntary muscle (8). There is abundant support for: 1) the existence of adenosine in other tissues and its increase with an increase in the ratio of

oxygen need to oxygen supply in the tissue; 2) the dilator potency of the nucleoside in several circulations; 3) the effectiveness of agents, which antagonize adenosine, in suppressing certain autoregulatory hyperemias; and 4) the effectiveness of other chemicals, which augment the circulatory actions of the nucleoside, in enhancing the same autoregulatory hyperemias (8). Most, if not all, of the evidence favoring the role of adenosine as a local, metabolic regulator of mesenteric blood flow has its parallel in research reports about other regional vascular beds.

#### ADENOSINE AND AUTOREGULATORY PHENOMENA

Mealtimes pose the major, physiological challenges, which confront the digestive system and its circulation. Within a matter of minutes, the sight, smell, and taste of food, and the motions of chewing and swallowing the food activate extrinsic and intrinsic autonomic nerves and release gastrointestinal, mucosal hormones and tissue substances. Many of these endogenous neurocrine, endocrine, and paracrine agents have a vasodilator effect on the mesenteric circulation (2, 3, 36, 57, 76—78). Some notable examples of these dilator compounds are VIP (79), CCK (80), and histamine (81). More important, collectively, these endogenous stimuli initiate or increase the following gastrointestinal functions: gastric and biliary emptying; peristaltic and segmental contractions of the small intestine; secretory activity of the stomach, pancreas, liver, and gut; the active absorption of glucose, galactose, amino acids,  $\text{Na}^+$ , and  $\text{Ca}^{++}$ , and a considerable outburst of metabolic activity (82). Not surprisingly, there is a dramatic increase in gastric and intestinal blood flows at mealtimes, with the former being a more sudden but transient hyperemia and the latter more gradual but sustained (83, 84).

In a plethora of reports, in which experiments were performed on either conscious animals ingesting a meal or anesthetized animals with nutrients placed in the intestinal lumen, postprandial hyperemia of the mesenteric circulation was observed in the gut of the dog (3, 9, 11, 31, 36, 79, 83, 85—97), rat (27, 29, 38, 98, 99), and pig (81, 100, 101). In each species, the postcibal increase in mesenteric blood flow was found in both anesthetized and conscious animals. In rats, direct comparison showed that the hyperemia was proportionately greater in the waking state than under anesthesia, probably because anesthetization blunts vascular reactivity and reduces vagal influences (57). Where such measurements were determined, mesenteric oxygen consumption was also found to increase with the presence of nutrients in the intestinal lumen (9, 31, 36, 82, 86, 87, 90, 92, 93, 100—103). Most, if not all, of the increment in oxygen uptake was attributable to the augmented blood flow, inasmuch as investigators noted either a smaller increase in oxygen extraction

than in blood flow (36, 89, 90, 92, 93, 101—102), or no change (82, 86, 100), or even a small reduction in tissue extraction of oxygen (90) during postprandial hyperemia. Furthermore, in a comparison of fed gut loops versus fasted loops, it was found that the major factor responsible for increased oxygen delivery was an increase in blood flow; in the fed gut, the ratio of oxygen availability to oxygen demand by the tissue was low (89). The converse situation applied in the fasted gut, in which the ratio of oxygen availability to tissue demand for oxygen was higher, and the dominant mechanism for providing more oxygen was an increase in tissue extraction of oxygen (89). Additionally, fed gut exhibited a much more pronounced pressure-flow autoregulation than did fasted gut (85). Postprandial hyperemia was also associated with increases in the capillary filtration coefficient (63), the density of perfused capillaries in the nutrient circulation (92, 93, 102), and the distribution of blood flow to the intestinal mucosa (93). Inasmuch as the bulk of the foregoing studies, in which postprandial hyperemia was demonstrated, utilized a constant pressure preparation, calculated mesenteric vascular conductance was increased (or calculated vascular resistance was decreased) during the hyperemia (10).

Although there appears to be considerable agreement about the measurable events transpiring during postprandial hyperemia (for which a student of this subject may be thankful), there are at least 2 major, troublesome matters about postprandial hyperemia which await resolution. Earlier in this review, note was taken of the discrepancy between responses of the mesenteric circulation to the entry of nutrients into the lumen of the gut and the vascular responses to adenosine reported from some laboratories. In particular, the reported depressant effect of adenosine on oxygen consumption by the gut and its diversion of blood flow away from the nutrient circulation of the mucosa (if correct) raise questions about this nucleoside as the metabolic regulator of the mesenteric circulation (2). However, it should be noted that other reports did not confirm the antimetabolic effect of adenosine (17, 33, 93) and that different receptor antagonists of adenosine prevented postprandial hyperemia in the canine gut, elicited by digested food and bile (9, 11). It is, of course, possible that 8-phenyl theophylline may have interfered with hyperemia by a mechanism unrelated to its blockade of adenosine receptors.

In the evaluation of another putative vasodilator metabolite in the gut, namely prostacyclin (which is a potent vasodilator substance generated originally by the action of phospholipase C on membrane phospholipids), a skeptical conclusion was drawn (102), similar to that expressed about adenosine (2). Prostacyclin prompted a mesenteric hyperemia, which was associated with a compensatory decrease in oxygen extraction and no change in either oxygen consumption or the density of perfused capillaries (102). By contrast, intraluminal perfusion of an isosmotic glucose and saline solution elicited a comparable hyperemia, which was associated with increases in

oxygen extraction, oxygen consumption, and the density of perfused capillaries (102). Also, suppression of the prostacyclin-generating enzyme system with cyclooxygenase inhibitors enhanced both the hyperemia and the elevated oxygen consumption, which followed instillation of digested food and bile in the jejunal lumen (87). Conversely, administration of arachidonate inhibited postprandial hyperemia (104).

There may be other metabolites, which assume a vasoregulatory role during postprandial hyperemia (3). Some of these putative metabolic vasodilators include cyclic AMP (53), ATP (54),  $K^+$  (2), histamine (3), tissue hypoxia (105), and tissue hyperosmolarity during absorption (106). In addition, there is evidence supporting modulation of postprandial hyperemia by unmyelinated, afferent, enteric nerves, which release the neuropeptide, VIP (29, 79, 99), although local neuroregulation of intestinal blood flow has been questioned (107). Enteric, peptidergic nerves also appear to be involved in cyclic AMP-induced intestinal secretion, another function of the gut, in which hyperemia would be anticipated (16, 108).

A second, puzzling body of observations about postprandial hyperemia relates to the enhancing effects of bile on the vasodilator response to different digestion products in the intestinal lumen. The 2 principal functions of bile acids in the digestive system are to emulsify ingested fats, in order to facilitate the digestion of lipids by water-soluble lipases, and to form micelles containing the bile acids and the products of digested lipids, in order to facilitate the passive absorption of those products across the membrane of the intestinal microvillus. Instillation of bile, in isosmotic saline, into the jejunal lumen has no effect on local blood flow (3, 79, 88), and infusion of bile or taurocholate into the ileal lumen actually decreases blood flow to that part of the gut (88, 109). Yet, commingling of bile with oleate, greatly enhances the small hyperemic response one would otherwise observe with the lipid digestion product alone (88). This finding might be explained on grounds that micelles containing oleate and bile acids accelerate the passive absorption of oleate, which in some arcane way signals a local hyperemia to accelerate transport of the absorbed product into the body. It should be noted, however, that bile acids are not absorbed from the lumen of the jejunum and that oleate is not transported into the blood. Furthermore, bile also markedly enhances the modest hyperemias prompted by instillation of glucose, glutamate, and aspartate into the jejunal lumen (86, 88), despite its playing no known role in their absorption. In addition, there is evidence that the absorption of glucose appears to increase vascular perfusion through both exchange vessels and resistance vessels of the microcirculation, whereas absorption of oleate seems to increase perfusion only through resistance vessels (90). Nevertheless, addition of bile to luminal solutions containing either glucose or oleate greatly enhances the postprandial hyperemias elicited by either nutrient (3, 90, 91).



The role of mediator for adenosine in other splanchnic autoregulatory events has also been explored, although not as extensively as in the case of postprandial hyperemia. Previously, in this review, the autoregulatory phenomenon in the liver, known as the hepatic artery "buffer reaction", was inferred to be adenosine-mediated. This conclusion was based upon results from experiments, in which potent adenosine receptor antagonists, such as 8-phenyl theophylline, prevented or greatly impeded the hyperemic response of the hepatic artery to a severe reduction in portal vein blood flow (64, 66, 67, 69). These receptor antagonists have also been found to suppress both pressure-flow autoregulation in the hepatic artery (64) and the increase in vascular resistance within the superior mesenteric artery, following elevation of portal venous pressure (22). There does not appear to be a myogenic mechanism in the hepatic buffer reaction (67). Additionally, there is evidence for the existence of adenosine receptors on the hepatic artery, which exhibits autoregulation, but not on the portal vein, whose flow is not autoregulated (63). There is also an autoregulatory restoration of total blood flow in the liver to long term infusions of the nucleoside itself (62).

Pressure-flow autoregulation in the superior mesenteric artery consists of the response of blood flow or vascular resistance to an experimentally imposed, sustained reduction in perfusion pressure in either constant pressure or constant flow preparations (2, 4, 78, 110). Initially, in a constant pressure preparation, the flow decreases abruptly, as the pressure is diminished, but then climbs back toward the control blood flow value, despite the maintained, lower perfusion pressure. The local vasodilation prompted by a decreased arterial pressure may be sufficient in the fed gut to cause mesenteric blood flow to exceed the control value, despite the sustained hypotension — a phenomenon termed "superregulation" (85, 89). Usually, in eliciting pressure-flow autoregulation, the perfusion pressure is reduced by decrements of 5 or 10 mmHg and held at each lower pressure for 5 min, while the blood flow response is observed. Eventually, a pressure is reached at which autoregulation of flow fails to occur; this is about 65—75 mm Hg (85). These determinations permit plotting a pressure-flow autoregulatory curve for the mesenteric circulation in order to study a variable such as the effects of adenosine receptor antagonists on the curve. Based on such analyses, it was found that mesenteric pressure-flow autoregulation was prevented or markedly inhibited by adenosine receptor antagonists (9, 20, 22, 23, 41). It was also concluded from the potency of these receptor antagonists, in suppressing this form of autoregulation, that myogenic mechanisms are not significant in mediating the recovery of blood flow from a decrement in perfusion pressure (20, 22, 23). Similarly, myogenic factors were discounted in 2 other mesenteric autoregulatory events, namely, the increased resistance, which follows elevation of mesenteric venous pressure (84), and reactive hyperemia (22). A possible role for histamine has

also been suggested in mesenteric pressure-flow autoregulation (41), analogous to its role in renal pressure-flow autoregulation (111).

Following short-term (30—120 sec) occlusion of the superior mesenteric artery, there is an abrupt increase in blood flow (50—150%) upon release of the occlusion (2, 5, 112). This “reactive hyperemia” lasts for a few min before blood flow returns to the preocclusion value. In several reports, reactive hyperemia was inhibited considerably by 8-phenyl theophylline (20, 22, 113), adenosine deaminase (113), and theophylline (9), but not by aminophylline (21). Furthermore, measurements of the concentration of adenosine in the venous effluent from feline gut loops at the peak of the postocclusion hyperemia indicated a 4-fold increase, compared with the preocclusion value (32).

Blood flow through the superior mesenteric artery is reduced dramatically by either electrical stimulation of perivascular sympathetic nerves or by intraarterial infusion of norepinephrine. These experimental manipulations are used to evoke 2 additional mesenteric autoregulatory phenomena: 1) “autoregulatory escape”, which is observed during sympathetic nervous stimulation or norepinephrine infusion, when blood flow shows considerable recovery from the vasoconstriction, despite continued adrenergic stimulation (2, 6, 7, 114); and 2) “post stimulation hyperemia”, which is observed immediately following cessation of the aforementioned forms of adrenergic stimulation, when blood flow increases by about 25% over the control value (2, 6). These phenomena appear not to depend upon adenosine mediation in the mesenteric circulation. Thus, there are reports that 8-phenyl theophylline failed to inhibit either escape (20) or post stimulation hyperemia (10, 20, 39) and that adenosine decreased the latter event (10), although adenosine deaminase did inhibit escape from norepinephrine-induced vasoconstriction (39). By contrast, depletion of neuropeptide transmitters from unmyelinated, afferent nerves in the gut greatly inhibited escape from sympathetic nerve stimulation (114). In an unrelated autoregulatory response, aminophylline failed to prevent the mesenteric hyperemic response to distension of the gut (115).

Finally, systemic and splanchnic hemodynamic responses have been reported during parenteral infusions of adenosine sufficient to provoke a sustained arterial hypotension of 50 mmHg in anesthetized dogs and pigs (18, 30). Major effects of the systemic administration of this nucleoside included decreased vascular resistance in the general arterial and mesenteric circulations, increased cardiac output and portal vein blood flow, decreased intestinal oxygen consumption, and increased hepatic oxygen uptake.

## CONCLUSIONS

As one surveys the criteria by which a physiological, intestinal vasodilator metabolite should be judged, it appears that the preponderance of evidence

favors the candidacy of adenosine moderately well. However, absolute proof of its mediation of autoregulatory hyperemias is still in the offing. The evidence supporting the candidacy of the nucleoside as a local regulator of mesenteric hyperemias, prompted by different experimental challenges, may be summarized, as follows:

1. Adenosine is present in the tissue of the gut in measurable quantities, which have been shown, in a few instances, to increase with the stimulus of either an enhanced metabolism or a diminished oxygen supply.
2. Adenosine is a potent dilator of mesenteric resistance vessels, when the nucleoside is administered exogenously into the circulation.
3. Blockade of adenosine receptors in the mesenteric circulation with synthetic antagonists interferes significantly with 3 autoregulatory phenomena, i.e., postprandial hyperemia, pressure-flow autoregulation, and reactive hyperemia, as well as with the hepatic artery buffer response.

The evidence which weakens the case for adenosine includes: a) findings in several reports that intraarterially infused adenosine depressed intestinal oxygen consumption and diverted blood flow away from the mucosal nutrient circulation; b) the unexplained role of bile as an adjuvant in postprandial hyperemia elicited by the intestinal transport of nutrients, in whose digestion or absorption bile plays no known role; c) the failure of adenosine receptors to inhibit some autoregulatory hyperemias of the gut; and d) the rather limited amount of evidence regarding tissue adenosine release in autoregulatory hyperemias, e. g., the most frequently cited report about this phenomenon is an abstract published over one dozen years ago (32).

Among these findings, the most difficult to reconcile with the proposed vasoregulatory role of endogenous adenosine is the first one cited, namely that exogenously administered adenosine evoked metabolic effects, which are contrary to those observed in postprandial hyperemia. However, there are 2 considerations, which temper this finding. First, there are also reports, which indicated that exogenous adenosine enhanced oxygen uptake and the perfusion of exchange vessels in the microcirculation of the intestinal mucosa. Second, even if exogenously administered adenosine evoked a mesenteric hyperemia, in which oxygen consumption and blood flow through the mucosal nutrient capillaries were reduced, as opposed to the findings in postprandial hyperemia, there may be a reasonable explanation. In postprandial hyperemia, it is assumed that there is a restricted, local release of endogenous adenosine into the interstitium close to the hypermetabolic, mucosal enterocytes. In this instance, the nucleoside would be acting as a paracrine substance specifically on the nearby smooth muscle of precapillary sphincters and arterioles in the superficial mucosa. Such effects of adenosine would increase local capillary perfusion and supply oxygen to metabolically active cells of the villi. In the case of the intraarterial infusion of adenosine into the gut, on the other hand, the

major effect is a diffuse relaxation of smooth muscle in resistance vessels throughout the intestinal wall, most of which is metabolically much less active than the enterocytes of the villi. This vascular effect would favor diversion of blood flow into metabolically inert regions, such as the muscularis, which comprise much of the intestinal wall. Under these conditions, one would expect adenosine to provoke a reduction in oxygen uptake. Obviously, research remains to be performed before the story of adenosine and the mesenteric circulation is more certain.

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Author's address: E. W. Jacobson, Departments of Medicine and Physiology, University of Colorado School of Medicine, 4200 East 9th Avenue, Denver, Co. 80262, USA.