

RESEARCH REVIEW

Regulation of Intestinal Blood Flow

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The gastrointestinal system anatomically is positioned to perform two distinct functions: to digest and absorb ingested nutrients and to sustain barrier function to prevent transepithelial migration of bacteria and antigens. Alterations in these basic functions contribute to a variety of clinical scenarios. These primary functions intrinsically require splanchnic blood flow at both the macrovascular and microvascular levels of perfusion. Therefore, a greater understanding of the mechanisms that regulate intestinal vascular perfusion in the normal state and during pathophysiological conditions would be beneficial. The purpose of this review is to summarize the current understanding regarding the regulatory mechanisms of intestinal blood flow in fasted and fed conditions and during pathological stress. © 2000 Academic Press

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VASCULAR ANATOMY AND DISTRIBUTION OF INTESTINAL BLOOD FLOW

The gastrointestinal system of mammals is supplied by three direct branches of the aorta: the celiac artery, the cranial or superior mesenteric artery, and the caudal or inferior mesenteric artery [1]. The celiac artery supplies blood flow to the stomach, liver, and spleen, while the superior mesenteric artery, the largest single branch of the abdominal aorta, supplies the entire small intestine, proximal portions of the colon, and the pancreas. The inferior mesenteric artery delivers blood flow to the distal colon. Total blood flow through these

arteries is typically 20–25% of cardiac output in the unfed state [2]. There is extensive overlap or collateral circulation in the distal vascular distributions of these arteries. During nutrient absorption, blood flow in each of these arteries is increased sequentially as the digestive chyme passes over the mucosal surface supplied by the particular arteries [3]. Following nutrient absorption, the blood flow to each segment returns to baseline levels as the chyme moves past that region of the digestive tract [4, 5]. This postprandial increase in blood flow is independent of organ distention and is solely dependent on the composition of the chyme [6, 7].

The intraorgan distribution of blood flow within the tissue layers of the intestine is not uniform [3] and appears to correspond to the functional importance of the tissue layer. In unfed animals at rest, blood flow to the mucosal layer is about 70–80% of total flow, while the muscular and serosal layers collectively receive 15–25% of organ flow and the submucosal layer is perfused by less than 5% [3]. Of the mucosal blood flow, approximately 60% perfuses the vessels that terminate as end loops and that supply the epithelial cells in the intestinal villi. The remaining 40% supply flow to the crypts and goblet cells [3]. The arterial microvascular branching pattern of the intestinal microvasculature, described by Bohlen and Gore [8, 9], is diagrammed in Fig. 1. Following the ingestion of a meal, blood flow increases by as much as 200% above baseline levels and persists for 2 to 3 h. This increase in flow is shifted to the mucosal layer by a process of capillary recruitment where existing but closed vessels open. The control mechanism of this recruitment process is unknown for the intestinal microcirculation. In the resting or unfed state only 20–30% of capillaries are normally perfused [1, 3]. The intestinal mucosa is the site of nutrient absorption; the submucosa, which consists of

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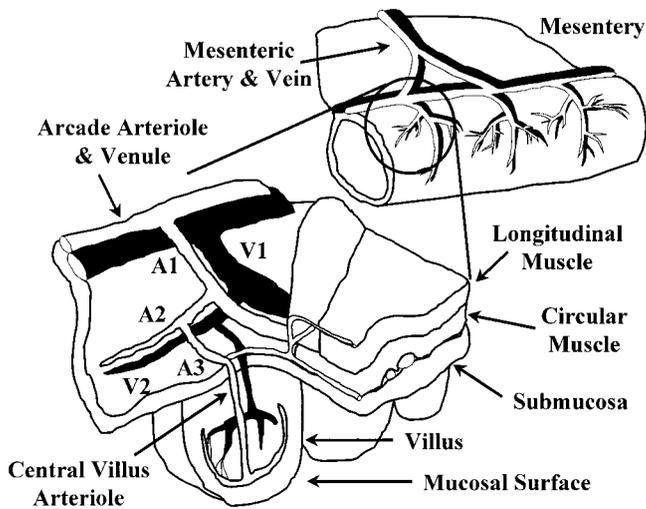


FIG. 1. Outline of the intestinal microvasculature emphasizing the mucosal blood supply with the inflow (A1), transitional (A2), and pre-mucosal (A3) arteriolar structure as well as outflow (V1) and transitional (V2) venules.

glandular cells, produces serous and mucous secretions, as well as newly formed, immature enterocytes; and the muscular layers provide contractile force for intestinal mixing and propulsion of the chyme. In general, blood flow to these three layers is autoregulated by metabolic factors such as decreased PO_2 , pH, or osmolarity and increased PCO_2 or adenosine. These mechanisms serve to maintain or increase blood flow to meet the tissue's need for oxygen and nutrient delivery and waste removal [10].

In addition to vascular perfusion, the organs of the gastrointestinal system contain numerous lymph vessels [11–14]. The gastrointestinal lymphatic circulation is anatomically divided into two separate partitions, which remain separate until they exit from the intestine near the mesenteric arcade vessels [12–14]. These two lymphatic circulations are termed the mucosal–submucosal lymph system and the muscular lymph system [12]. The mucosal–submucosal lymph circulation functions to drain the absorbed nutrients and metabolic by-products from the villi during digestion. These villus lymph vessels, termed lacteals, do not have smooth muscle cells. However, it is thought that the muscularis mucosa, which lines the villi beneath the epithelial cells, can contract in synchrony with the relaxation of the muscular layers of the intestine, thereby propelling lymph from the villi into the submucosal arcade of lymph capillaries [15]. The enteric nervous system coordinates the contractions of villi in this process to optimize lymph drainage from the intestine and to facilitate nutrient entry into the circulation [12, 13].

The contraction of the muscularis mucosa occurs along the length of the villus and propels lymph toward the submucosal arcade vessels, which are located prox-

imal to the site where the mucosal–submucosal and muscular lymph systems unite [13, 14]. As lymph collects in the submucosal arcade, the contraction of the longitudinal and circular muscular layers during the digestion of chyme propels the lymph out from the intestinal layers and into the outflow lymph vessels [13, 14]. These outflow lymph vessels exhibit typical characteristics of lymph vessels including rhythmic contractions and unidirectional valves, which function to propel the lymph and to prevent retrograde flow back toward the intestinal layers. These larger lymph vessels are lined with endothelial cells and smooth muscle cells that produce mediators of smooth muscle tone in response to different nutrients or metabolic products present in the lymph [12, 13]. The role of lymph-derived mediators in regulation of resting vascular tone or postprandial hyperemia is not known, but involvement has been implicated in some studies [16].

FACTORS THAT REGULATE RESTING VASCULAR TONE

In the unfed resting state, numerous mechanisms exist that control vascular tone in the microvessels of the gastrointestinal circulation. Table 1 provides a summary of mechanisms and mediators that might contribute to resting tone, and Fig. 2 provides a theoretical scale to indicate the relative contribution of the different vasoactive mediators as a function of position in the arterial tree. Constriction of large arteries and arterioles ($>50 \mu\text{m}$) is primarily under the influence of neural regulation from the vasomotor center of the

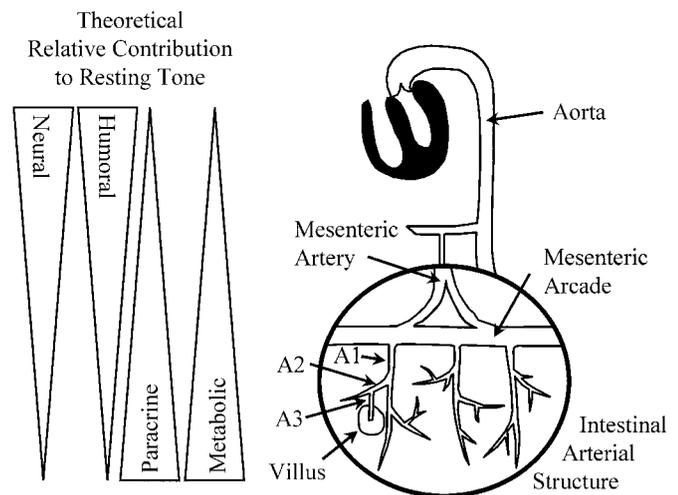


FIG. 2. Theoretical contribution to vascular tone of the mediators from the classification system outlined in Table 1 as a function of their position in the vascular tree. Neural and humoral agents might contribute more to the tone of large conduit blood vessels, while paracrine and metabolic mediators contribute proportionally more to the smaller microvessels due to limited diffusion into systemic blood.

TABLE 1
Potential Vasoactive Mediators of the Enteric Circulation

Constrictors	Dilators
<i>Neural Mediators</i>	
↑ Sympathetic tone (Adrenergic) ↓ Parasympathetic tone (Cholinergic) Neuropeptide Y	↓ Sympathetic tone ↑ Parasympathetic tone Substance P Vasoactive intestinal polypeptide (VIP) Calcitonin gene-related peptide (CGRP α)
<i>Circulating Humoral Mediators</i>	
Catecholamines (except in liver and muscle) Angiotensin II Vasopressin Serotonin Activated complement (C5a)	Catecholamines (only in liver and muscle) Histamine Bradykinin Activated complement (C3a, C5a) Adrenomedullin
<i>Circulating Paracrine and Autocrine Mediators</i>	
Endothelin-1 (vascular smooth muscle cells) Platelet-activating factor Constrictor prostaglandins (F $_{2\alpha}$)	Endothelium-derived relaxing factor (EDRF, NO) Endothelium-derived hyperpolarizing factor (EDHF) Dilator prostaglandins (I $_2$ or prostacyclin) Endothelin-1 (endothelial cells)
<i>"Metabolic" Vasodilators</i>	
↑ PO $_2$ ↓ PCO $_2$ ↑ pH ↓ Metabolites (K $^+$, lactate, adenosine, etc.)	↓ PO $_2$ ↑ PCO $_2$ ↓ pH ↑ Metabolites

medulla oblongata through preganglionic sympathetic neurons of the intermediolateral area of the spinal cord. This neurogenic input to the large blood vessels and inflow arterioles is primarily sympathetic, with α -adrenergic (vasoconstriction) control more prevalent than β -adrenergic (vasodilation) influence [17, 18]. These pathways are well described and will not be elaborated on in this review. Previous studies [10] suggest that metabolic autoregulation plays a significant role in the regulation of resting vascular tone in the enteric circulation. Autoregulation by decreased PO $_2$, pH, or osmolarity and increased PCO $_2$ or adenosine exerts significant local environmental control of microscopic blood vessel tone. Other studies [16, 19] indicate a near-constant oxygen delivery to the mucosal surface, while the mean inflow pressure varied from 30 to 120 mm Hg. The extent to which other mediators and mechanisms listed in Table 1 contribute to resting vascular tone in the intestine varies and has not been completely defined.

CONTROLLING FACTORS IN THE REGULATION OF POSTPRANDIAL HYPEREMIA

Postprandial intestinal hyperemia is defined as an increase in blood flow to the gastrointestinal system

during the digestion and absorption of nutrients. This hyperemia is a complex response mediated by neural, humoral, and paracrine elements [20–22]. As early as 1910, Brodie and colleagues [23, 24] demonstrated increased blood flow in isolated canine intestinal segments after the placement of a peptone solution into the lumen of the intestine, while placement of differing molar strengths of saline solutions did not produce a similar response. Studies in the 1930s with newly developed electromagnetic flow probes [25, 26] demonstrated an intestinal postprandial hyperemia in conscious instrumented dogs following the intraluminal placement of a predigested meal. Since these initial observations, additional experiments have focused on the mechanisms of absorptive hyperemia, and yet the basic control mechanisms have not been completely elucidated [20]. Traditional thought proposes that postprandial hyperemia is a functional response that exists to maintain adequate blood flow for preservation of intestinal function and integrity during digestion and absorption [20].

In the 1970s and 1980s, Chou and others [20] performed a seminal series of experiments to clarify the role of the intestinal luminal contents in postprandial hyperemia, which has been extensively reviewed pre-

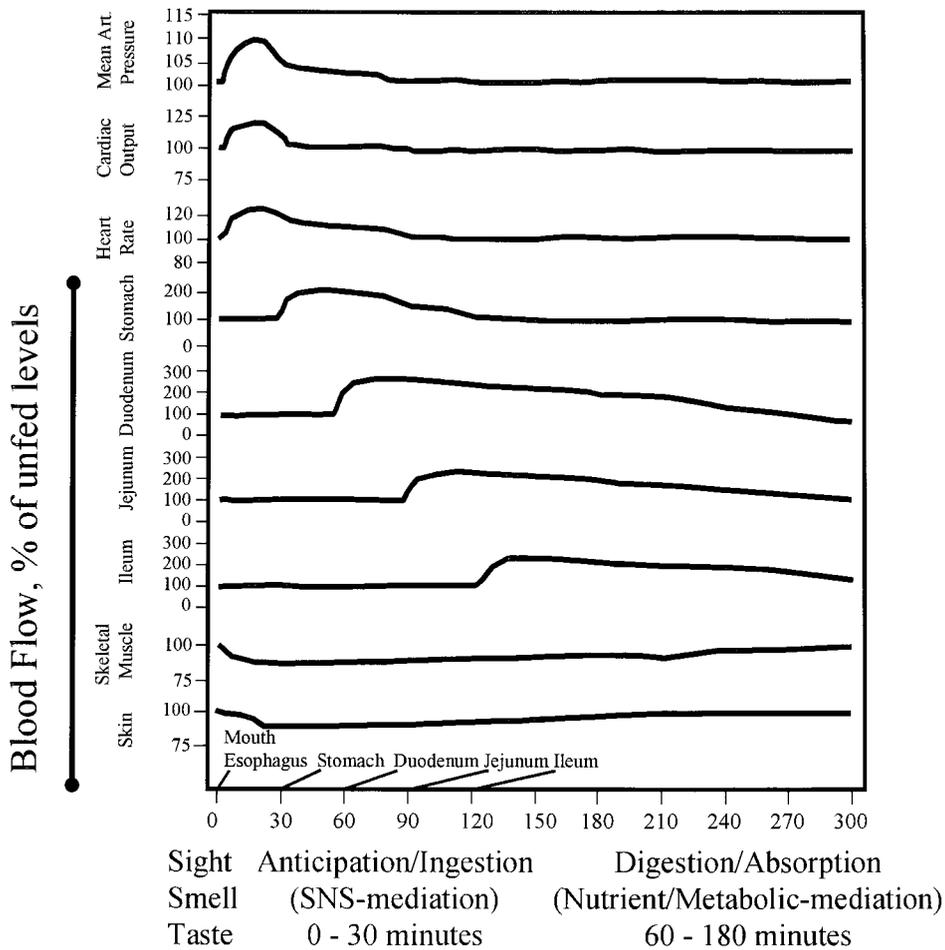


FIG. 3. Descriptive summary of the results from numerous studies depicting the cardiovascular responses during postprandial hyperemia. Blood flow increases in specific organs as digestive chyme reaches that organ. Indications along the time axis mark the point at which the chyme reaches the stomach, duodenum, jejunum, and ileum to initiate the metabolically mediated digestion and absorption stages of postprandial hyperemia.

viously. This review highlights key elements and describes the known hierarchy of nutrient inducers of hyperemia. Lipids and fats in combination with bile salts are the most potent nutrient inducers of increased flow, followed by glucose and other carbohydrates, proteins, peptides, and amino acids as the least potent nutrient inducers. A combination of these various compounds [6, 27, 28] produces the greatest increase in intestinal blood flow, and bile salts further increase flow during nutrient digestion and absorption [29, 30].

During the digestion of a meal, there are four activities that occur during two well-described cardiovascular stages: anticipation and ingestion, and digestion and absorption [20, 22]. Anticipation and ingestion occur simultaneously for a brief period and are followed by simultaneous digestion and absorption over a much longer duration [20]. The anticipation and ingestion phases, mediated by the sympathetic nervous system [4], increase cardiac output, blood pressure, heart

rate and splanchnic and renal vascular resistance, and decrease carotid artery resistance, with a variable response in skeletal muscle and skin vascular resistance depending on the initial status of the individual [4, 5, 31]. The cardiovascular components of the digestion and absorption stages begin as the stomach fills with chyme and typically coincide with the end of anticipation and ingestion [7, 20]. Digestion and absorption of nutrients from the intestine produce segment-specific increases in blood flow that persist as long as chyme remains in that intestinal segment [7, 32]. In this way, blood flow increases first to the stomach, then to the duodenum, jejunum, and ileum in order, as the chyme passes through the gastrointestinal tract over time (Fig. 3). The increase in flow to the digestive organs is compensated by both a decrease in flow to other organs (skeletal muscle and perhaps skin) and an increase in cardiac output [4, 33]. The occurrence of both events is suggested, since renal blood flow also increases following absorption of a protein-rich meal [5].

Chou and Coatney [20] systematically analyzed the potency of various nutrients to stimulate postprandial hyperemia. These experiments first demonstrated that the liquid phase of the luminal contents of predigested, mixed-composition meals were responsible for the increased flow, even in the absence of a solid phase [6, 7, 34]. In contrast to this finding, the placement of a liquid saline solution or the solid phase of a predigested meal alone did not produce hyperemia [7, 34]. These findings suggested that the compound(s) responsible for postprandial hyperemia exists in the hydrolytic products of food digestion. To further elucidate the mechanisms underlying these phenomena, investigators analyzed the ability of individual nutrients in the liquid phase to produce increased intestinal blood flow, as measured by the radiolabeled microsphere technique in isolated and/or intact canine intestine.

Based on those studies, the single most potent nutrient-mediator of intestinal hyperemia when administered alone is glucose [29, 35–39], and glucose-induced ileal hyperemia is attenuated by the presence of bile salts [6, 29, 30]. However, glucose-induced jejunal hyperemia is not affected by the addition of bile to the intestinal injectate [6, 29]. Next in degree of potency are various long-chain fatty acids such as oleic acid and caproic acid. When administered to isolated intestinal segments alone, oleic acid produces a mild hyperemia, but a mixture of oleic acid and bile produces the greatest increase in flow, surpassing that of mixed glucose and bile in the ileum [6, 28–30]. Bile interacts with lipids in the intestinal lumen to form lipid micelles, the absorption of which is thought to provide the potency of lipid/bile mixtures to produce increased flow [6, 29, 39]. Proteins and products of protein digestion are the least potent in producing increased intestinal flow states, especially when administered in the physiological amounts that are present during the digestion of a high-protein meal [6, 39]. However, certain amino acids are known to cause vasodilation in the intestinal circulation. The amino acids glutamine, aspartate, and glycine produce hyperemia when administered to the lumen of isolated intestinal segments at pharmacological doses [6, 29, 39]. Other studies show that luminal distention, mechanical mucosal stimulation alone, and extrinsic innervation by either sympathetic or parasympathetic neurons are not required for hyperemia to occur [6, 40].

POTENTIAL MECHANISMS FOR POSTPRANDIAL HYPEREMIA

Several factors have been proposed as potential mediators of postprandial hyperemia. The classification system of Chou and Coatney [20] subdivides potential mediators into five broad categories: direct effects of absorbed nutrients, enteric nervous system effects and reflexes, gastrointestinal hormones and peptides, local

nonmetabolic vasoactive mediators, and local metabolic vasoactive mediators.

Involvement of components from each of the five categories has support in the literature as contributing to the complex mechanisms of postprandial hyperemia. It is interesting to note that all of the proposed mechanisms of nutrient absorption and transport require increased oxygen delivery. Bohlen [41, 42] demonstrated that intestinal villus PO_2 decreased from 15–20 mm Hg in unfed rats to less than 5 mm Hg during nutrient-induced hyperemia. Other studies show that lipid micelles, carbohydrates, and amino acids use oxygen for absorptive metabolism. Lipid micelle transport requires the largest increase in oxygen delivery [42–46] followed by sodium-linked absorption of carbohydrates and di- and tripeptides and amino acids [41, 42]. In contrast to these oxygen-dependent phenomena, villus lymph and interstitial fluid osmolarities increase from resting, unfed levels of 400 mOsm to 600 mOsm or more during the absorption of nutrients [16, 47]. Studies [12, 35] show increased diameters of inflow A1 and A2 arterioles and increased arteriolar flow in response to the injection of hyperosmolar solutions into submucosal arcade lymph vessels, which might involve nitric oxide [48]. Conversely, intraluminal injections of isosmotic solutions have no effect on blood flow [12, 35]. The findings of these studies have led to the hypothesis that both oxygen-dependent and osmolarity-dependent metabolic mechanisms contribute to the initiation, development, and maintenance of postprandial hyperemia.

DIRECT EFFECTS OF ABSORBED NUTRIENTS

Some nutrients in the chyme are themselves vasodilators in the intestinal microcirculation, such that sufficient quantities of these compounds can produce vasodilation after they enter the circulation. Intraarterial injection of carbohydrates including glucose and most amino acids does not alter microvascular flow in the intestine [27]. However, micellar solutions, which contain bile and oleic acid, caproic acid, or taurocholate, increase flow in the jejunal circulation when administered intraarterially [28], as can bile salts alone [30]. In addition to lipid micelles and some amino acids, luminal carbon dioxide and hydrogen ions can diffuse across the intestinal epithelial barrier directly to initiate metabolic autoregulation of blood flow in the intestinal microvessels [33, 49].

ENTERIC NERVOUS SYSTEM EFFECTS AND REFLEXES

The potential role of the enteric nervous system in postprandial hyperemia is not clear, since it has been well demonstrated that extrinsic sympathetic and parasympathetic innervation is not required for postprandial hyperemia [40, 45, 50]. However, the role of

nonadrenergic, noncholinergic neurons cannot be excluded because some studies have shown that stimulation of mucosal mechanoreceptors enhances a glucose-induced increase in intestinal blood flow [27, 40, 51]. Also, the topical anesthetic dibucaine can block glucose-induced and oleic acid-induced hyperemia, presumably because dibucaine prevents epithelial cell uptake of glucose and oleic acid micelles by altering membrane fluidity [40]. Capsaicin-sensitive afferent neurons (C-fibers) that release neurotransmitters such as cholecystokinin (CCK), substance P, and vasoactive intestinal polypeptide (VIP) might also be involved, since capsaicin and lidocaine can prevent the jejunal hyperemia that is associated with micelle absorption [52]. This latter mechanism is credible since VIP release has been demonstrated in response to placement of oleic acid-bile micelles into the jejunum [53].

GASTROINTESTINAL HORMONES AND PEPTIDES

A number of gastrointestinal hormones have vasoactive properties, but their involvement in postprandial hyperemia is not clear because the levels that have been measured experimentally are lower than the minimum doses required to produce vasodilation [20]. Gastrin, VIP, CCK, substance P, secretin, gastric inhibitory polypeptide (GIP), neurotensin, calcitonin-gene related peptide α (CGRP- α), glucagon, enkephalins, somatostatin, and peptide YY do not appear to have a role in postprandial hyperemia at physiological doses [53–56]. On the other hand, it is possible that local sites in the intestine might experience sufficient levels of these compounds to produce a controlled local effect, but such phenomena have not been demonstrated to date. Thus, on a whole-organ scale, these compounds probably are not involved in nutrient-induced absorptive hyperemia.

LOCAL NONMETABOLIC VASOACTIVE MEDIATORS

The small intestine is capable of releasing serotonin [57], histamine [58], bradykinin [59], and prostaglandins [51, 60–62] in response to a wide range of physiological and pathophysiological stimuli. These mediators might enhance, diminish, or have no effect on nutrient-induced absorptive hyperemia, depending on the initial state of the animal and the presence of arachidonic acid in the intestinal chyme. For example, blockade of cyclooxygenase to prevent intermediate formation of prostanoid vasoconstrictors (thromboxane A_2 or prostaglandin $F_{2\alpha}$) enhances nutrient-induced hyperemia in normal canine jejunum [63–65], while arachidonate loading inhibits the hyperemia [63–65]. Prostanoid synthesis occurs in the jejunum [66], and following placement of predigested food into the intestinal lumen, prostaglandin (PG) synthesis increases ($PGE_2 > PGI_2 > thromboxane A_2 > PGF_{2\alpha}$) [51]. How-

ever, the exact role of these autocooid mediators probably depends on other factors [51] such as the relative balance of prostanoid vasoconstrictors and vasodilators at rest and stimuli for the gut to produce histamine, bradykinin, or serotonin. Histamine, bradykinin, and serotonin (at low concentrations) are potent vasodilators in the intestinal microcirculation, and histamine blockade of H_1 but not H_2 receptors diminishes the hyperemic response to the placement of predigested food in the jejunum [67].

LOCAL METABOLIC VASOACTIVE MEDIATORS

As previously noted, intestinal blood flow is precisely regulated via metabolic mechanisms to provide the right amount of blood flow for the metabolic needs of the tissue [10, 37, 68]. In fact, most if not all of the mechanisms of intestinal blood flow regulation alter the oxygen use by tissues involved in nutrient absorption. In general, any mechanism that increases the amount of hyperemia also increases the oxygen debt of the villi, while those mechanisms that diminish hyperemia result in less oxygen uptake and utilization. Thus, it is difficult to disentangle such a complex relationship, but the current paradigm suggests that oxygen uptake and tissue PO_2 are the initial mediators of postprandial hyperemia.

In addition to PO_2 and tissue osmolarity, other metabolic products increase in the intestine during postprandial hyperemia, in particular hydrogen ions [69–71] and adenosine [72–75]. Adenosine is a ubiquitous vasodilator that occupies a unique position in most metabolic processes as a component in energy storage in the form of adenosine triphosphate (ATP) and also in the key second messenger system of cyclic adenosine monophosphate (cAMP). During the process of energy-dependent sodium-linked absorption of carbohydrates or amino acids by the epithelium, adenosine is released into the villus interstitial space and portal circulation. It is known that adenosine is transiently increased in the portal circulation during the first 3 to 11 min immediately preceding the increased blood flow and oxygen uptake by the mucosal tissue [75]. Other studies [76–79] also support the finding that adenosine is an important mediator of nutrient-induced hyperemia.

Recently, the role of nitric oxide (NO) as a key regulator of intestinal motility, fluid balance, and electrolyte absorption has been demonstrated [80–82]. These findings have prompted the investigation of a potential role for nitric oxide in postprandial hyperemia. NO is a potent endothelium-derived vasodilator that directly enters vascular smooth muscle cells to induce relaxation. Our studies [83] have demonstrated that glucose-induced premucosal arteriolar vasodilation in the rat ileum is competitively blocked by *L*- ω -nitroarginine methyl ester (*L*-NAME), which inhibits both constitutive (NOS-3) and inducible (NOS-2) nitric

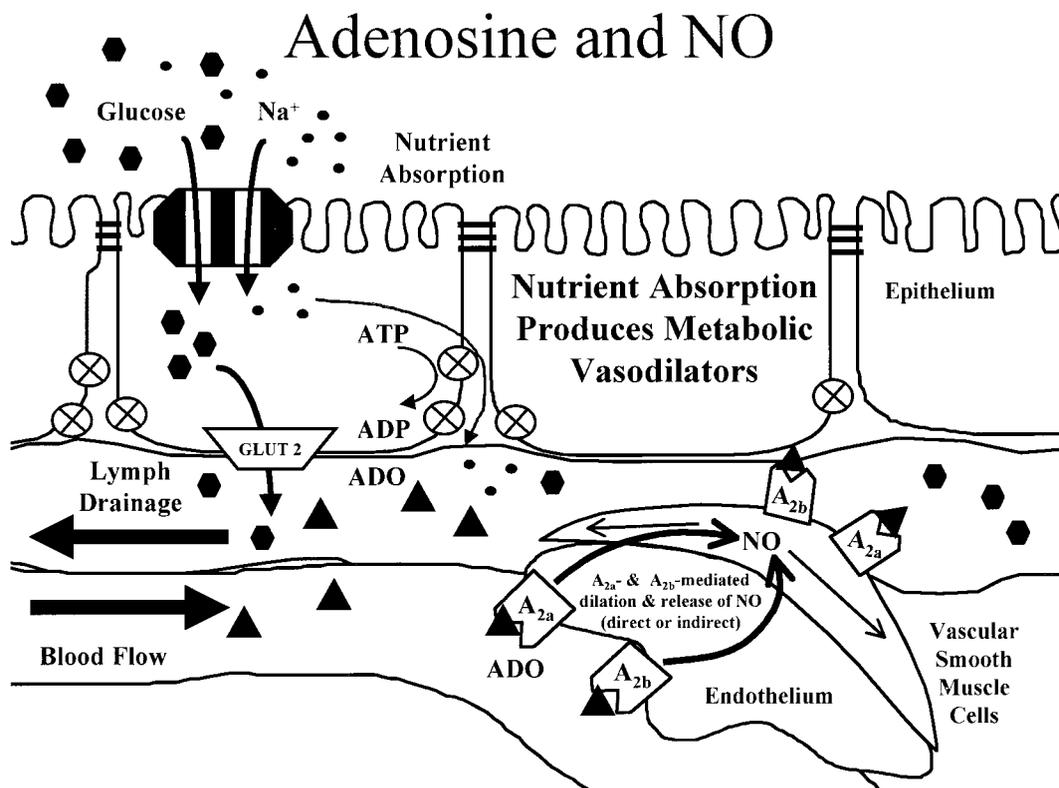


FIG. 4. Schematic overview of the proposed mechanism of adenosine-mediated nitric oxide release during postprandial hyperemia. Briefly, this diagram summarizes the Na^+ -linked absorption of glucose, which is thought to increase ATP utilization and stimulate the production of the potent metabolic and paracrine vasodilators adenosine and nitric oxide.

oxide synthase enzyme isoforms. Thus, in a rodent model NO appears to be essential for premucosal arteriolar dilation during topical glucose exposure. These observations, along with studies that document adenosine involvement in nutrient-induced intestinal hyperemia, suggest a possible relationship between the two compounds.

We have recently studied the role of adenosine in the generation of elevated nitric oxide metabolite (NO_x) levels in response to intestinal epithelial nutrient exposure [84]. Adenosine A_{2a} and A_{2b} are G-protein-associated transmembrane receptors, which produce vasodilation via increased intracellular cAMP levels by activation of adenylate cyclase [85]. Thus, adenosine receptors might also be capable of increasing intracellular Ca^{2+} via phospholipase C activation with subsequent influx of extracellular Ca^{2+} . Numerous studies [86–92] suggest a synergistic relationship between adenosine and nitric oxide. Recent experiments demonstrate that intragastric glucose placement increases portal NO metabolite levels and that adenosine A_2 receptors are required for this glucose-induced NO response [84]. Adenosine A_{2b} receptor activation is essential for portal vein NO elevation, while adenosine A_{2a} receptor activation appears to augment or secondarily regulate portal NO_x production [unpublished

data]. Gastric gavage with L-glutamine also resulted in increased portal nitric oxide metabolite levels dependent on adenosine A_{2b} receptors, while oleic acid gavage and racemic glycine gavage had no effect on portal NO metabolite levels [84]. These studies implicate the existence of an adenosine–nitric oxide signaling mechanism in the glucose- or glutamine-induced generation of postprandial hyperemia (Fig. 4). This signaling mechanism might involve Na^+ -linked, secondary active transport mechanisms, since both D-glucose and L-glutamine are absorbed in this way.

PATHOPHYSIOLOGICAL ALTERATIONS IN THE CONTROL OF INTESTINAL BLOOD FLOW

A number of pathophysiological conditions exist that alter intestinal macro- and microcirculatory regulatory mechanisms such that these alterations in intestinal blood flow could contribute to the genesis or maintenance of the disease processes. The mechanisms that produce these conditions are difficult to elucidate because of the involvement of many physiological systems and mediators with multiple effects in different organ systems. The remainder of this review summarizes the pathological alterations associated with regulation of microvascular tone in the conditions of septic

shock, hemorrhagic shock, cardiogenic shock, and portal hypertension. The effect of mechanical bowel obstruction on the intestinal microvasculature has not been studied by intravital microcirculatory methods and is therefore not included in this review.

SEPTIC SHOCK

Infectious shock in humans is often characterized by an early hyperdynamic, high-cardiac-output phase followed by a delayed hypodynamic, low-cardiac-output period, and can sometimes lead to multiple-organ dysfunction syndrome (MODS) and death [93]. In laboratory models of systemic septicemia or bacteremia, the gut has been implicated as the motor or generator of MODS [93, 94]. The gut might contribute to the progression of MODS by a combination of gut-associated immune alterations [95] and impairment of intestinal blood flow during systemic inflammation. If mucosal blood flow decreases below a critical level for cellular viability, free radical generation, cytokine production, and perhaps the loss of tissue integrity and mucosal barrier function can occur [96]. In hyperdynamic shock states, mucosal vascular perfusion appears to be compromised, despite decreased total peripheral resistance and increased cardiac performance [97]. Hinshaw [98] reviewed the myriad microcirculatory changes that occur following sepsis, including impaired coagulation status, diminished red blood cell deformability, increased microvascular permeability and subsequent tissue edema, altered distribution of blood flow, altered microvascular responses to adrenergic mediators (smooth muscle function), and impaired endothelial cell function. The endothelial cell occupies a central position in the cascade of events that lead to impaired vascular function during bacteremia or septicemia, and a number of vasoactive compounds with altered regulation during sepsis have been identified. This review focuses on arachidonic acid metabolites, cytokines, oxygen-derived free radicals (ODFRs), endothelin 1, platelet-activating factor, adrenomedullin, and nitric oxide.

Using intravital videomicroscopy techniques, Gosche *et al.* [99] examined the involvement of arachidonic acid metabolites in the microvascular alterations of infection. The authors found that *Escherichia coli* bacteremia increases cardiac output and decreases intestinal blood flow secondary to arteriolar and venular constriction. Cyclooxygenase blockade with mefenemate does not improve arteriolar diameters or blood flow, but profoundly dilates venules, suggesting that microvascular control mechanisms in response to a septic challenge vary considerably, not only by organ system, but also by distal-to-proximal position in the arteriolar and venular vascular trees. Clearly, experimental sepsis models produce intestinal microvascular vasoconstriction and hypoperfusion [100–102]. This

phenomenon might lead to the generation of ODFRs and altered cytokine production. Using intravital videomicroscopy techniques, Krysztopik *et al.* [103] have recently demonstrated protection against intravenous *E. coli*-induced intestinal arteriolar vasoconstriction and hypoperfusion [103] and impaired renal blood flow [104] by intravenous lazaroid antioxidant that protectively scavenges ODFRs and prevents lipid radical chain reactions. The vasoconstriction in both inflow and premucosal arterioles was prevented without altering the hyperdynamic cardiac response, suggesting that local intestinal ODFR production might play a role in the intestinal microvascular sequelae following a bacteremic challenge.

Endothelins are potent vasoconstrictor polypeptides with a range of other effects, including control of renal function; neuroendocrine stimulation of atrial natriuretic peptide, renin, aldosterone, and catecholamines; and control of gastrointestinal blood flow. Endothelin 1 gene expression is upregulated in a mouse model of cecal ligation and puncture [105], and in a rat model of *E. coli* bacteremia using intravital videomicroscopy, endothelin 1 is implicated in the shift toward a more tonically constricted state [106]. The upregulation and expression of adhesion molecules (or cytokines) [107] with altered neutrophil trafficking and subsequent capillary and/or postcapillary venule plugging constitute another endothelial-dependent mechanism that might contribute to impaired intestinal blood flow. These changes could further contribute to hypoxic conditions that could stimulate free radical formation and proinflammatory cytokine production.

Platelet-activating factor (PAF) is another potential mediator of blood flow that has been shown to be upregulated during infection [108, 109]. Bar-Natan *et al.* [110] compared the microvascular events of early *E. coli* bacteremia in the absence and presence of the PAF receptor antagonist WEB2086 with direct topical application of PAF on the intestinal surface in intravital videomicroscopy experiments. A decrease in arteriolar inflow and venular outflow was noted in both sepsis and PAF-treated groups with spatially discrete areas of venular constriction in the group treated with topical PAF. Application of the PAF receptor antagonist prevents the sepsis-induced vasoconstriction and reduction in blood flow in both the PAF-treated group and the infected group.

Recent studies [111–114] suggest that adrenomedullin, a potent vasodilatory peptide derived from endothelial cells, might play an early role in the development of both increased cardiac output and decreased total peripheral resistance during the early hyperdynamic phase of septic shock. These studies [113] demonstrate increased levels of adrenomedullin in the serum of rats 2 h after cecal ligation and puncture (CLP) associated with elevated levels of adrenomedullin

mRNA in the small intestine, the left ventricle, and the thoracic aorta [111, 113]. The time course observed in this expression pattern correlates well with the previously described cardiovascular phases of septic shock [114]. Additionally, adrenomedullin blockade with specific anti-rat adrenomedullin antibodies prevents the development of the hyperdynamic phase of sepsis and normalized microvascular blood flow 5 h after the onset of CLP [112]. Direct intravital videomicroscopy studies to examine the contribution of adrenomedullin to microvascular tone in the intestinal microcirculation have not been reported.

Animal studies demonstrate that nitric oxide is chronically elevated during infection and that NO synthase blockade might improve survival rate [115]. However, early videomicroscopy studies [116, 117] suggest that NO blockade during acute *E. coli* bacteremia worsens microvascular constriction and hypoperfusion. The effect of continued overexpression of NO on endothelial and vascular smooth muscle cells is not clear [118]. Vascular ring studies have shown decreased reactivity of large conduit blood vessels after prolonged infectious exposure [119–121]. Spain *et al.* [122] addressed this issue by studying *in vivo* intestinal microvascular responses shortly after intravenous *E. coli* infusion and observed impaired magnitude and frequency of vasomotion, a normally occurring rhythmic process of dilation and contraction, in both inflow and pre-mucosal arterioles. Topical application of acetylcholine partially restores the vasomotor activity of the pre-mucosal arterioles and fully restores the vasomotion of the inflow arterioles. There is no change in sensitivity or reactivity of endothelium-dependent relaxation to acetylcholine or endothelium-independent relaxation to nitroprusside during bacteremia. However, constriction with norepinephrine is impaired in bacteremia in both inflow and pre-mucosal arterioles, suggesting that acute bacteremia causes both endothelial alterations (vasomotion) and vascular smooth muscle cell changes (α -adrenergic constriction).

HEMORRHAGIC SHOCK

Resuscitated hemorrhagic shock in the absence of any infectious challenge or other complication can result in death, despite the restoration of cardiac performance and central hemodynamic variables. In the intestinal circulation resuscitated hemorrhagic shock produces vasoconstriction and hypoperfusion in a fashion similar to that previously described for septic shock [123]. The endothelial cell appears to play a pivotal role in the development of this low-flow condition. The interpretation of laboratory studies of vascular function following resuscitated hemorrhagic shock has been complicated by the use of a wide range of experimental hemorrhagic shock models and protocols. Different

methods of hemorrhage significantly alter the development, severity, and outcome of the hemorrhage.

Studies by Chaudry and co-workers [124] and others [123, 125, 126] reveal that microvascular blood flow in the liver, small intestine, kidneys, spleen, and skeletal muscle are significantly impaired, despite the restoration of central venous pressure and central hemodynamic parameters of cardiac function and arterial pressure. Numerous studies [123–126] establish that intestinal microvascular blood flow is significantly impaired following hemorrhage and resuscitation, despite the confirmation of adequate fluid resuscitation by the measurement of cardiac performance and blood pressure. Intravital videomicroscopy studies indicate that diameters of inflow and pre-mucosal arterioles return to normal values immediately following resuscitation, but arteriolar constriction progressively worsens thereafter with an accompanying decrease in blood flow. Spain *et al.* [127] demonstrate impaired endothelial-dependent vasodilation to acetylcholine in these vessels, as well as histologic injury and neutrophil influx and impaired nitric oxide synthase function, but no apparent oxidant injury. Furthermore, these changes are prevented or diminished by the blockade of the complement cascade with soluble complement receptor treatment prior to resuscitation. The mechanism of this microvascular protection is not known, but it might involve protection of endothelial cell function and/or decreased neutrophil activation and influx.

Several studies [128, 129] show that pentoxifylline administration during and after resuscitation improves microvascular tissue perfusion. Pentoxifylline has a wide range of therapeutic benefits after hemorrhage and resuscitation, which include improved cardiac performance and intestinal and renal microvascular blood flow. Pentoxifylline is thought to improve these conditions by one of its myriad effects, including increased red blood cell deformability, endothelial cell membrane fluidity, and altered neutrophil activity and cytokine production. It is not known which of these functions produces the improvement in microvascular blood flow, or if all of the effects are necessary for microvascular perfusion to be restored to prehemorrhage levels.

In addition to pentoxifylline and soluble complement receptor, heparan sulfate [125] and chemically modified heparin [130], which are heparin analogues with little or no anticoagulant activity, also appear to restore microvascular blood flow after centrally resuscitated hemorrhagic shock. These agents appear to similarly protect the endothelial cell membrane after hemorrhagic shock, suggesting that the endothelium plays a central role in the pathogenesis of altered vascular responsiveness to resuscitated hemorrhagic shock.

CARDIOGENIC SHOCK

Alterations in microvascular control mechanisms during low-cardiac-output cardiogenic shock have not been extensively studied by microcirculation research methods. However, Bulkley *et al.* [131, 132] have clearly demonstrated that a porcine model of cardiogenic shock (pericardial tamponade induced by 10% dextran injection into the pericardial cavity) significantly increases celiac artery resistance, compared with either baseline or total peripheral resistance, by an angiotensin II-mediated mechanism. In these studies, the addition of captopril, an angiotensin-converting enzyme inhibitor, selectively prevents the increase in celiac artery resistance, while the addition of angiotensin II in normal pigs mimics many of the changes seen with pericardial tamponade. Two additional studies have examined microvascular blood flow using laser Doppler flowmetry in similar porcine models of cardiogenic shock induced by pericardial tamponade. In the first [133], investigators found diminished microvascular blood flow in the mesentery that persisted throughout the experimental protocol. Treatment with an angiotensin-converting enzyme inhibitor after the onset of cardiogenic shock restored mesenteric microvascular blood flow to near-normal levels. A second study [134] examined the effectiveness of pulsatile blood flow during low-cardiac-output shock at maintaining microvascular perfusion as assessed by laser Doppler flowmetry. Pulsatile blood flow maintained microcirculatory perfusion better than the nonpulsatile perfusion. These latter findings suggest a potential role of endothelial cell derangement with impaired perfusion and decreased tissue oxygenation during cardiogenic shock secondary to systemic alterations in the renin-angiotensin system.

PORTAL HYPERTENSION

A number of elegant studies have examined the microcirculatory effects of portal hypertension on the intestinal and gastric circulations. Benoit and Granger [135] have described a model of portal venous hypertension using chronic graded stenosis of the portal vein that produces portal hypertension and slightly decreased systemic pressures resulting in increased centerline red blood cell velocity in inflow A1 arterioles with no change in A1 diameter. While this model produced no difference in A1 or A2 diameters or flow, the A3 arterioles displayed significantly elevated pressure that was carried through to the outflow V1 veins. The increased intestinal microvascular pressure associated with portal hypertension is caused by both reduced arteriolar resistance to flow and venous congestion from impaired portal vein drainage. Tarnawski *et al.* [136] also demonstrated altered gastric mucosal architecture (compressed cytosolic area of endothelial cells,

increased pinocytotic vesicle area, and increased thickness of the capillary basement membrane) by transmission electron microscopy after staged ligation of the portal vein. Further studies [137] to examine the gastric microvascular alterations to portal hypertension demonstrate a biphasic response in gastric vessel diameter, flow, and wall thickness. By Day 15 after portal vein constriction, the vessels were severely dilated with decreased wall thickness and impaired flow.

Later studies by Joh *et al.* [138] revealed significantly increased vascular reactivity to norepinephrine after staged prehepatic portal vein stenosis in the inflow arterioles of rat intestine, while the transitional A2 and premucosal A3 arterioles showed decreased reactivity to norepinephrine. However, these alterations in α -adrenergic reactivity did not alter the diameters of the inflow arterioles. The contribution of norepinephrine, vasopressin, and angiotensin II to resting tone in the intestine is altered after chronic portal hypertension. Norepinephrine primarily contributes to resting vascular tone in the A3 arterioles in portal hypertension, while vasopressin contributes primarily to A1 tone and angiotensin II contributes only to A3 tone. Circulating levels of vasopressin and angiotensin II are increased, suggesting that the increased contribution of these mediators to resting tone might be related to increased production rather than increased receptor sensitivity. To examine the pathogenesis of the impaired reactivity to norepinephrine following portal hypertension, Wu and Benoit [139] compared norepinephrine reactivity after acute or chronic portal hypertension, sham operation, or portocaval shunting. Norepinephrine receptor reactivity is altered in a biphasic pattern in acute (decreased NE reactivity) versus chronic portal hypertensive (increased NE reactivity) animals. Additionally, the portocaval shunt animals exhibit increased reactivity to α -adrenergic stimulation, suggesting that the alterations in adrenergic reactivity might be due to redistribution of microvascular blood flow rather than to the elevated microvascular pressures previously observed in the A3 arterioles through the V1 venules.

Recent studies [140] examined the deleterious microvascular effects of propranolol, which is often used in the treatment of cirrhotic hypertension, on the intestinal microcirculation and demonstrated that the cardiovascular actions of propranolol were caused primarily by β_2 -adrenergic blockade. In a rat model of progressive prehepatic portal venous shunting, propranolol treatment resulted in microvascular vasoconstriction and reduced blood flow, which was manifested in both normals and portal hypertensive animals. These changes were reversed with phentolamine treatment, indicating β_2 -adrenergic receptor involvement in the propranolol-induced vasoconstriction. Wu and Benoit [141] also studied the involvement of the cAMP and

cGMP second-messenger pathways in the altered reactivity to norepinephrine from portal hypertension. These studies involved the blockade of cAMP-dependent protein kinase A by the addition of Rp-cAMPS, a cAMP analogue, or the blockade of cGMP via LY-83583. Rp-cAMPS had no effect on microvascular parameters in normal animals, but during portal hypertension PKA blockade significantly decreased A1 blood flow and restored norepinephrine reactivity. On the other hand, guanylate cyclase blockade had no effect on any measured variable in normal or portal hypertensive animals. Therefore, portal hypertension appears to impair norepinephrine reactivity via cAMP-dependent alterations in the intestinal microvasculature.

NUTRIENT ABSORPTION AND SHOCK

Several studies [142–145] suggest that nutrient exposure and/or absorption in the gastrointestinal system improves outcome in some pathophysiological conditions. Numerous investigators have proposed that certain nutrients such as L-glutamine, L-arginine, ω -3 fatty acids, and RNA fragments, when administered enterally, provide more therapeutic benefit than the same nutrients applied intravenously. These findings have led to the use of terms such as immunonutrition and immune-enhancing enteral diet, since these nutrients are thought to directly feed immune cells, particularly those found in gut-associated lymphoid tissue. An alternative hypothesis to explain some of the benefits of early enteral feeding is that these nutrients might provide a greater stimulus to enhance mucosal blood flow during nutrient absorption than isocaloric, isonitrogenous control diets that do not contain these nutrients. The maintenance of mucosal perfusion might then serve to protect intestinal epithelial cell function as well as mucosal microvascular endothelial cell oxygenation. Traditionally, intravital microscopy studies have used glucose-free bath or suffusate solutions to avoid the effects of nutrient exposure on intestinal microvascular control. Only two studies have examined the role of nutrient absorption on intestinal microvascular blood flow in shock states [126, 146] using intravital microscopy methods. The first study found that glucose exposure and/or absorption maintained intestinal blood flow during *E. coli* bacteremia and the second found that glucose protected intestinal blood flow following resuscitated hemorrhage. As suggested previously [84], this protection might involve the generation of adenosine and/or nitric oxide during the nutrient absorption process, both of which are powerful vasodilators that could increase mucosal blood flow.

SUMMARY

Intestinal blood flow is regulated to provide adequate blood flow to maintain the supply of oxygen and essential nutrients to the tissue and to remove waste products. The predominate mechanisms at rest involve metabolic control by oxygen, H^+ , and carbon dioxide as well as other metabolic regulators such as lactate and adenosine. The placement of nutrients into the intestinal lumen initiates nutrient-dependent hyperemic mechanisms, which appear to be initiated by the generation of mucosal oxygen debt due to increased metabolic activity during nutrient absorption. Glucose, the most potent single mediator of postprandial hyperemia, appears to initiate a mechanism that involves adenosine-mediated NO production. Various pathophysiological conditions appear to produce endothelial cell dysfunction via different mechanisms that result in impaired mucosal microvascular blood flow. Many of these alterations seem to involve the endothelial cell membrane, and treatments that protect this membrane might provide protection against impaired microvascular blood flow and tissue hypoxia. In certain conditions, nutrient absorption early after traumatic injury might play a protective part in the maintenance of intestinal blood flow, endothelial cell stability and mucosal barrier function.

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