Current Concepts in Gastric Microcirculatory Pathophysiology

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When the barrier to acid back-diffusion is disrupted, there is a protective increase in gastric mucosal blood flow to help remove the back-diffusing acid. Only recently has the mechanism for calling forth this protective hyperemia been determined. The gastric mucosa and submucosa are innervated by many capsaicin-sensitive sensory nerve fibers containing vasodilator peptides. The gastric mucosal sensory neurons monitor for acid back-diffusion, and, when this process occurs, signal for a protective increase in blood flow via release of calcitonin gene-related peptide from the submucosal periarteriolar fibers.

The endothelium-derived vasodilator, nitric oxide, plays an important role both in the maintenance of basal gastric mucosal blood flow and in the increase in blood flow that accompanies pentagastrin-stimulated gastric acid secretion. It also interacts with the capsaicin-sensitive sensory nerves in the modulation of the microcirculation to maintain mucosal integrity.

Finally, it has been shown that neutrophils play an important role in various forms of mucosal injury. The leukocytes adhere to the vascular endothelium and contribute to injury by reducing blood flow via occlusion of microvessels, as well as by releasing mediators of tissue damage.

In recent years, there has been a significant increase in our knowledge of mechanisms of control of the gastric microcirculation and the role of the microcirculation in gastric mucosal injury. This paper will briefly review three of the newer concepts in gastric microcirculatory pathophysiology: the role of the gastric mucosal sensory nerves, the role of the endothelium-derived vasodilator nitric oxide, and the role of the neutrophil.

ROLE OF SENSORY NERVES IN THE GASTRIC HYPEREMIC RESPONSE TO ACID BACK-DIFFUSION

Most tissues would rapidly disintegrate if exposed to the corrosive acid that bathes the gastric mucosa. The gastric mucosal barrier [1], however, prevents acid from entering and damaging that tissue. It has long been recognized that disruption of this barrier, with resultant increased acid back-diffusion, is accompanied by an increase in gastric mucosal blood flow (GMBF). This increase in flow is thought to dilute, 677

Abbreviations: BSA: bovine serum albumin  CGRP: calcitonin gene-related peptide  EDNO: endothelium-derived nitric oxide  EDRF: endothelium-derived relaxing factor  EDTA: ethylenediaminetetraacetic acid  GMBF: gastric mucosal blood flow  iv: intravenous(ly)  L-NAME: NO\(\text{\textsuperscript{O}}\)-nitro-L-arginine methyl ester  L-NMMA: NO\(\text{\textsuperscript{O}}\)-monomethyl-L-arginine  NO: nitric oxide  NOS: nitric oxide synthetase  NSAID: non-steroidal anti-inflammatory drug  sGC: soluble guanylate cyclase

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neutralize, and carry away the back-diffusing acid [2-4], thereby protecting the tissue from injury. The organization of the gastric circulation requires submucosal arterioles to be dilated in order to increase GMBF [5]. Thus, the message of increased acid entry must be transmitted over the 500 μm distance that separates the mucosal surface from the submucosal arterioles. The gastric mucosa and submucosa are innervated by many capsaicin-sensitive sensory nerve fibers containing vasodilator peptides. It has been shown that activation of these fibers by intragastric capsaicin increases GMBF [6] and prevents gross and histological injury caused by ethanol [7] or acidified aspirin [8]. Because of these observations, Holzer et al. [9] postulated that these chemosensitive afferent neurons mediate the blood flow response to acid back-diffusion.

They tested this hypothesis in an anesthetized rat preparation, using the hydrogen gas clearance technique, in order to measure gastric mucosal blood flow, and a continuous gastric perfusion technique, in order to measure acid back-diffusion [9]. When the gastric perfusate was changed from saline to 0.15 N HCl, there was no change in basal GMBF, but there was a slight loss of acid from the lumen. In contrast, as shown in the upper panels of Fig. 1, barrier disruption by 15 percent ethanol in the presence of 0.15 N HCl resulted in a significant and sustained increase in GMBF and (not shown) a marked increase in disappearance of acid from the gastric perfusate. Only mild gross damage and minimal deep histologic injury of the
corpus mucosa developed, however. When the same experiment was performed in rats that had had functional ablation of the capsaicin-sensitive sensory neurons by systemic pre-treatment with high-dose capsaicin, the findings were quite different (lower panels of Fig. 1). The sensory denervation had no effect on basal GMBF, but the hyperemic response to acid back-diffusion was completely lost (even though, not shown, there was just as marked an acid back-diffusion). In addition, there was a significant increase in both the area of gross mucosal damage and the percentage length of tissue section with deep histologic injury.

The above-described study provided strong evidence that the capsaicin-sensitive sensory neurons in the gastric mucosa play an important role in monitoring for an acid influx that might threaten the integrity of the mucosa. When these neurons sense an increase in acid influx, they signal the submucosal arterioles to dilate in order to increase blood flow into the mucosa to prevent deep and extensive mucosal injury.

The capsaicin-sensitive sensory fibers in the gastric submucosa densely innervate the submucosal blood vessels. These nerve fibers contain a variety of peptides, including substance P, calcitonin gene-related peptide (CGRP), neurokinin A, and VIP [10–12]. Among these peptides, CGRP is the most potent gastric vasodilator [13]. Gray et al. [14], as well as Holzer et al. [15], demonstrated that stimulation of the vascularly perfused stomach with low-dose capsaicin induced a large increase in the release of CGRP into the venous effluent. Furthermore, Lippe et al. [16] demonstrated that the close arterial administration of CGRP to the rat stomach prevented gross injury produced by 25 percent ethanol or acidified aspirin. These findings led to the hypothesis that CGRP is a major mediator of the gastric hyperemia induced by stimulation of capsaicin-sensitive sensory neurons.

Li et al. [17] tested this hypothesis in the anesthetized rat, using the same techniques employed by Holzer et al. [9]. The intra-arterial infusion of rat alpha-CGRP at a dose of 20 pmol/minute significantly increased GMBF by 45 percent. Prior close intra-arterial infusion of hCGRP8–37 (500 pmol/minute for ten minutes) completely blocked the exogenous CGRP-induced increase in GMBF, thus demonstrating the efficacy of this specific CGRP receptor antagonist [18]. The effect of CGRP receptor blockade during acid back-diffusion then was studied. After the measurement of basal GMBF, an intra-arterial infusion of hCGRP8–37 or its vehicle, bovine serum albumin (BSA), was started and continued for 20 minutes, and then the intragastric perfusion medium was changed to 0.15 N HCl plus 15 percent ethanol. Ten minutes after the start of intragastric perfusion of HCl plus ethanol, GMBF was again determined. Results are shown in Fig. 2. The receptor antagonist had no significant effect on basal GMBF, but it completely abolished the increase in GMBF in response to the intragastric perfusion with acidified ethanol. CGRP receptor blockade also resulted in a significant increase in both gross corpus mucosal injury (14.8 percent ± 2.6 percent versus 6.7 percent ± 1 percent in the BSA group) and deep histologic injury (49.4 percent ± 7.5 percent versus 30.2 percent ± 7.3 percent in the BSA group). Recently, Lippe and Holzer [19] showed that this CGRP-induced gastric mucosal hyperemia is prevented by inhibition of endothelium-derived nitric oxide, which suggests that CGRP vasodilation involves stimulation of release of endogenous nitric oxide.

These data provide strong evidence that CGRP, possibly acting via release of the endothelium-derived relaxing factor nitric oxide, is a major mediator in the gastric
hyperemic response to acid back-diffusion. With the inhibition of the hyperemic response to acid back-diffusion, either by sensory denervation or CGRP receptor blockade, gross and histological gastric mucosal damage is significantly aggravated. This finding adds to the evidence that the hyperemic response is an important protective mechanism against acid-induced injury.

ROLE OF THE ENDOTHELIUM-DERIVED RELAXING FACTOR NITRIC OXIDE

The existence of an endothelium-derived relaxing factor (EDRF) was unsuspected until the discovery by Furchgott and Zawadzki [20] of the importance of an intact endothelium in acetylcholine-induced vascular relaxation. They observed that, while acetylcholine produced graded relaxation of unrubbed isolated preparations of rabbit aorta, no relaxation occurred in preparations which had been rubbed to remove the endothelium. This first description of the phenomenon was confirmed by other laboratories, and it was also shown that a wide range of vasodilators release EDRF [21]. Subsequent studies demonstrated that EDRF had a half-life of about six seconds and, in this and other respects, was pharmacologically similar to nitric oxide. In 1987, it was established in independent studies by Palmer et al. [22] and Ignarro et al. [23] that EDRF indeed was nitric oxide (NO). It is known now that activation of the endothelial cell stimulates the production of endothelium-derived nitric oxide (EDNO) from L-arginine via the action of the enzyme nitric oxide synthetase (NOS). The nitric oxide diffuses into the vascular smooth muscle, where it activates soluble guanylate cyclase (sGC), resulting in the accumulation of cyclic guanosine monophosphate (cGMP). In turn, this process leads to cyclic GMP-dependent protein phosphorylation, which probably mediates the vasodilator action of EDRF [21]. Another important advance in studies of EDRF was the finding that L- (but not D-) analogs of arginine, by serving as a competitive substrate for NOS, inhibited the formation of
nitric oxide. The original EDRF studies were performed in vitro in large conductance vessels, such as the aorta, which play little or no role in regulating tissue flow; arterioles are the resistance vessels which control tissue blood flow. By using L-arginine analogs in vivo to inhibit NO formation throughout the vascular tree, the role of NO release from arterioles in the regulation of tissue blood flow could be studied. Endogenous NO now has been implicated in the regulation of resting GMBF. In addition, it appears to serve as a mediator for certain types of gastric hyperemia. Other mechanisms also play a role in the regulation of these and related gastric phenomena and have been shown to interact with NO.

**Role of Endogenous NO in Gastric Mucosal Blood Flow**

Pique et al. [24] used the L-arginine analog N°-monomethyl-L-arginine (L-NMMA) to investigate the role of endogenous NO in the modulation of gastric mucosal blood flow, as determined by the hydrogen gas clearance technique. The intravenous administration of 12.5–50 mg/kg induced a significant dose-dependent increase in systemic blood pressure, and a significant dose-dependent decrease in gastric mucosal blood flow (Fig. 3). The specificity of the analog effect was demonstrated by the inhibition of both the rise in blood pressure and the fall in GMBF by the concurrent administration of 100 mg/kg L-arginine, and the failure of the enantiomer, D-NMMA, to alter resting blood pressure or GMBF. Thus endogenous

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**FIG. 3.** Effects of iv L-NMMA, L-NMMA + L-arginine, or D-NMMA on resting systemic arterial blood pressure (BP) or gastric mucosal blood flow (GMBF) as estimated by hydrogen gas clearance in the anesthetized rat. Results, expressed as percentage change from the control values, are the means ± SEM of seven to eight rats per group, where statistical difference from control is shown as *p < 0.05. (Reprinted from [24] with permission of Elsevier Publishers.)
NO plays a role in the modulation of basal blood vessel tone in the gastric mucosal microcirculation.

Walder et al. [25] studied the role of NO as a possible mediator of the hyperemia that accompanies pentagastrin-stimulated acid secretion. Laser Doppler flowmetry was used to monitor GMBF. Pentagastrin, 750 ng/kg/minute intravenously (iv), produced an increase in mucosal blood flow within 30 seconds, and this hyperemia lasted throughout the ten-minute infusion period. Pre-treatment with L-NMMA, 1 mg/kg/minute for ten minutes, attenuated the increase in GMBF by 82 percent. Similar results were obtained by Piqué et al. [26], using the hydrogen gas clearance technique to measure GMBF and a continuous gastric perfusion technique to measure acid secretion. L-NMMA, 12.5 m/kg iv, had no effect on pentagastrin-(80 μg/kg/minute) stimulated acid secretion, but attenuated the accompanying increase in blood flow by 65 percent (Fig. 4). A larger dose of L-NMMA, 50 mg/kg iv, completely inhibited the increase in GMBF and slightly, but significantly, inhibited acid secretion. Thus endogenous NO not only modulates basal gastric vascular tone, but also is a mediator of the vasodilator response that accompanies stimulation of acid secretion. It does not appear, however, to have any direct effect on the stimulation of acid secretion.

**Interactions Between Endogenous NO and Other Mechanisms in the Maintenance of Gastric Mucosal Integrity and Resting Blood Flow**

The interactions between endogenous NO, endogenous prostacyclin, and sensory neuropeptides (released from capsaicin-sensitive neurons) in the maintenance of gastric mucosal integrity were investigated by Whittle et al. [27]. Acid saline (100 mM
HCl) was instilled into the gastric lumen of a pylorus-ligated, anesthetized rat. Administration of one of the three substances, L-NMMA to inhibit endothelium-derived NO formation, indomethacin to inhibit prostanoid biosynthesis, or chronic capsaicin pre-treatment to denervate the capsaicin-sensitive sensory nerves, alone did not induce acute mucosal injury in these rats. In capsaicin-pre-treated rats, however, L-NMMA dose-dependently induced acute mucosal damage. In indomethacin-pre-treated rats (5 mg/kg iv), L-NMMA also induced mucosal damage. Furthermore, following indomethacin administration in capsaicin-pre-treated rats, L-NMMA induced even greater damage than it did with either indomethacin- or capsaicin-pre-treatment alone. These findings indicate a role for endogenous NO acting in concert with endogenous prostaglandins and sensory neuropeptides in the modulation of gastric mucosal integrity.

Since the maintenance of gastric mucosal function and integrity depends critically on the status of the microcirculation, Tepperman and Whittle [28] then investigated the effect of these combinations of treatments on gastric mucosal blood flow, as measured by laser Doppler flowmetry in the anesthetized rat. N⁵-nitro-L-arginine methyl ester (L-NAME), a more potent inhibitor of NO biosynthesis, was used in this study. L-NAME induced a dose-dependent and significant fall in resting blood flow. A threshold dose of L-NAME, which had no effect on resting blood flow in the normal rat, did significantly decrease resting GMBF in capsaicin-pre-treated rats. Capsaicin-pre-treatment, however, had no effect on the hypertensive actions of L-NAME. Interestingly, indomethacin had no significant effect either on the fall in blood flow induced by L-NAME in capsaicin-pre-treated rats or on the hypertensive action of L-NAME in those rats.

These blood flow data provide evidence for an interaction of NO with endogenous sensory neuropeptides from capsaicin-sensitive afferent neurons in the modulation of the gastric microcirculation. The fact that the hypertensive actions of L-NAME were not significantly altered in capsaicin-pre-treated rats indicates that the interactions between endogenous NO and sensory neuropeptides are not generalized effects in all vascular beds. It is possible that this interaction contributes to the LNMA-induced acute mucosal injury in capsaicin-pre-treated rats. On the other hand, indomethacin had no effect on the blood flow changes induced by inhibition of NO synthesis in capsaicin-pre-treated rats, even though it augmented the mucosal injury in this situation [27]. This finding suggests that endogenous prostanoids do not interact with NO and sensory neuropeptides in the modulation of resting mucosal blood flow, yet do influence the tissue susceptibility to local ischemia [28].

**ROLE OF NEUTROPHILS IN GASTRIC MICROcirculatory PATHOPHYSIOLOGY**

As described in the review by Granger [29], there now is substantial evidence to support the hypothesis that xanthine oxidase-derived oxyradicals and granulocytes play a major role in ischemia-reperfusion microvascular injury. During the ischemic period, xanthine dehydrogenase is converted into xanthine oxidase. On reperfusion, the molecular oxygen brought to the tissue reacts with hypoxanthine and xanthine oxidase to produce a burst of superoxide anion and hydrogen peroxide. The latter, in turn, react with iron, via the Haber-Weiss reaction, to form the highly reactive hydroxyl radical, which initiates lipid peroxidation of cell membrane components with the release of substances that attract, activate, and promote the adherence of
granulocytes to the microvascular endothelium. The adherent neutrophils cause further cell injury of endothelial cells and, following diapedesis into the tissue, cause injury of parenchymal cells via release of superoxide anion and various proteases. *In vitro* studies have shown that activated neutrophils must adhere to endothelial cell monolayers to enhance paracellular permeability or to produce cell injury [30]. Analogous *in vivo* studies were performed by Hernandez et al. [31], in which either neutrophils were depleted using anti-neutrophil serum, or neutrophil adherence to the endothelial cell was blocked by the use of a monoclonal antibody directed against a specific membrane-associated glycoprotein that modulates neutrophil adherence to endothelium. Both neutrophil depletion and prevention of neutrophil adherence were equally effective in attenuating ischemia-reperfusion-induced increase in microvascular permeability in the small intestine.

Studies in the rat stomach have demonstrated an important role for neutrophils not only in hemorrhagic shock injury (an ischemia-reperfusion injury model) but also in ethanol and non-steroidal anti-inflammatory drug-induced injury.

**Hemorrhagic Shock**

Smith et al. [32] studied the effect of neutrophil depletion, by anti-neutrophil serum, on gastric mucosal injury and blood flow in rats subjected to 30 minutes of shock (hemorrhage to 27 mm Hg arterial pressure), followed by a 60-minute reperfusion period. Pre-treatment with anti-neutrophil serum reduced the number of circulating neutrophils by 95 percent, hemorrhagic shock-induced gross lesion area by 50 percent, and the clearance of $^{51}$Cr-labeled red blood cells into the gastric lumen by 80 percent. Blood flow was measured by the radiolabeled microsphere technique. Although neutrophil depletion did not affect basal or reperfusion blood flow in the stomach, blood flows in the ischemic (shock) period were significantly higher in the mucosa and submucosa of both the corpus and antrum. These data suggest that the neutrophils in this situation might be acting by adhering to the microvascular endothelium and increasing resistance to blood flow, thereby exacerbating the tissue hypoxia induced by hemorrhagic hypotension.

**Ethanol Injury**

Kvietys et al. [33] studied the effect of neutrophil depletion on the gastric mucosal injury produced by perfusing the lumen of the anesthetized rat’s stomach with progressively increasing concentrations of ethanol (10, 20, and 30 percent, each for 40 minutes). Mucosal injury was assessed by gastric clearance of $^{51}$Cr-labeled EDTA (ethylenediaminetetraacetic acid), which was injected intravenously at the start of each study. There was a marked dose-dependent increase in $^{51}$Cr-EDTA clearance from blood-to-gastric lumen with the ethanol perfusions, and this increasing clearance correlated with increasing histological damage. Neutrophil depletion significantly attenuated the gastric mucosal injury (Fig. 5A). Interestingly, the extent of the gastric mucosal protection was directly related to the severity of the neutropenia: the greater the neutropenia, the greater the protection (Fig. 5B). Oxyradicals did not seem to be involved in the injury, as treatment with superoxide dismutase, catalase, or inactivation of xanthine oxidase (by tungstate pre-treatment) did not offer significant protection against the injury. The authors postulated that ethanol, diffusing into the gastric tissue, stimulated the formation of proinflammatory compounds
that promoted the adherence of circulating neutrophils to the microvasculature and activated both resident and adherent neutrophils. The activated granulocytes generate oxyradicals and secrete various proteases. Since oxyradicals did not appear to be involved, the authors postulate that neutrophilic proteases may be the final mediators of the ethanol injury.
Non-Steroidal Anti-Inflammatory Drug (NSAID) Injury

Wallace and his colleagues [34,35] have provided strong evidence that gastric mucosal injury by NSAIDs is a neutrophil-dependent process. Rats made neutropenic by prior treatment with anti-neutrophil serum were found to be significantly more resistant to the gastric damaging actions of indomethacin or naproxen than were control rats [33]. This effect appeared to be due to the neutropenia and not to differences in inhibition of prostaglandin synthesis, as gastric cyclo-oxygenase activity was inhibited by over 95 percent in both normal and neutropenic rats which received indomethacin or naproxen. The investigators then used a rabbit model to examine the role of leukocyte adherence in the mechanism of the NSAID-induced gastropathy. Gastric damage was produced by intragastric instillation of indomethacin (5 gm/ml) for a period of 30 minutes. Histologic studies revealed vascular congestion and leukocyte margination within the mucosa (Fig. 6). Grossly, the indomethacin treatment caused the formation of numerous hemorrhagic lesions. In rats pretreated with a monoclonal antibody (IB-4) directed against adhesion molecules on the leukocyte, the extent of this damage was markedly reduced. The histologic injury, vasocongestion, and leukocyte margination also were markedly and significantly reduced. Thus leukocyte adherence to the gastric vascular endothelium appears to be an important factor in the pathogenesis of NSAID-induced gastric injury. The authors postulate that the leukocytes contribute to the mucosal injury by occluding microvessels, thereby reducing mucosal blood flow, and by releasing various mediators, proteases, and free radicals that can produce tissue necrosis.
CONCLUSIONS

The gastric mucosa and submucosa are innervated by many capsaicin-sensitive sensory nerve fibers containing vasodilator peptides. These fibers play an essential role in protecting the mucosa against acid back-diffusion injury. The gastric mucosal sensory neurons monitor for acid back-diffusion, and, when this condition occurs, signal for a protective increase in blood flow via release of calcitonin gene-related peptide from the submucosal periartheriolar fibers. Endogenous nitric oxide also is involved in this signaling mechanism. Whether it is released from the endothelium by CGRP and acts as the final dilator principle or acts as a neurotransmitter in the neural pathway between the mucosal and submucosal nerves remains to be determined.

The endothelium-derived vasodilating factor, nitric oxide, plays an important role both in the maintenance of basal gastric mucosal blood flow, and in the increase in blood flow that accompanies pentagastrin-stimulated gastric acid secretion. It also interacts with the capsaicin-sensitive sensory nerves in the modulation of the microcirculation to maintain mucosal integrity. The precise mechanism of this interaction, however, has not yet been worked out.

Recently it has been shown that neutrophils play an important role in various forms of mucosal injury. The leukocytes adhere to the vascular endothelium. It has been hypothesized that they contribute to injury by reducing blood flow via occlusion of microvessels, as well as by releasing mediators of tissue damage both within the microvessels and in the tissue after extravasating from the vessels.

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