

SPECIAL REPORTS AND REVIEWS

Neural Emergency System in the Stomach

PETER HOLZER

Department of Experimental and Clinical Pharmacology, University of Graz, Graz, Austria

The maintenance of gastric mucosal integrity depends on the rapid alarm of protective mechanisms in the face of pending injury. Afferent neurons of extrinsic origin constitute an emergency system that is called into operation when the gastric mucosa is endangered by acid and other noxious chemicals. The function of these chemoceptive afferents can be manipulated selectively and explored with the excitotoxin capsaicin. Most of the homeostatic actions of capsaicin-sensitive afferents are brought about by peptides released from their peripheral endings in the gastric wall. When stimulated, chemoceptive afferents enhance gastric blood flow and activate hyperemia-dependent and hyperemia-independent mechanisms of protection and repair. In the rodent stomach, these local regulatory roles of sensory neurons are mediated by calcitonin gene-related peptide acting via calcitonin gene-related peptide 1 receptors and neurokinin A acting via neurokinin 2 receptors, with both peptides using nitric oxide as their common messenger. In addition, capsaicin-sensitive neurons form the afferent arc of autonomic reflexes that control secretory and motor functions of the stomach. The pathophysiological potential of the neural emergency system is best portrayed by the gastric hyperemic response to acid backdiffusion, which is signaled by afferent nerve fibers. This mechanism limits damage to the surface of the mucosa and creates favorable conditions for rapid restitution and healing of the wounded mucosa.

Although the discovery of *Helicobacter pylori* and its eradication have revolutionized the understanding and management of peptic ulcer disease, knowledge of the pathophysiological mechanisms by which this bacterium weakens the defensive forces of the gastroduodenal mucosa lags behind. Gastric mucosal homeostasis is maintained by a multitude of physical, chemical, and physiological factors that collectively form the gastric mucosal barrier and, as such, prevent hydrogen ions from entering the tissue at quantities that produce cell injury.¹ The possibility that neurons constitute an important element in gastric mucosal protection from injury was hardly thought of, given that the vagus nerve has long

been considered to be a permissive factor in peptic ulcer disease. It was only recently that extrinsic afferent neurons were discovered to represent a neural emergency system in the digestive tract. By releasing peptide transmitters from their peripheral endings, these sensory neurons regulate a variety of functions that can be viewed as increasing the resistance of the tissue to injury and facilitating the repair of damaged tissue.

The discovery of these sensory neuron functions was made possible by capsaicin, a pharmacological tool with which the activity of certain primary afferent neurons can be manipulated selectively.² Capsaicin is an excitotoxin that acutely stimulates a group of afferent neurons with unmyelinated (C) or thinly myelinated (A δ) nerve fibers and, depending on the dose and route of administration, may cause a long-lasting defunctionalization of these neurons. The excitotoxic action is restricted to neurons with C- and A δ -fibers because only these cells (albeit not all) express receptor-binding sites (vanilloid receptors) for capsaicin and structurally related ligands.² By application of capsaicin to experimental gastroenterology it was unraveled that extrinsic afferent nerve fibers in the gut are of physiological and pathophysiological importance for mucosal homeostasis. The current article sets out to characterize the mechanisms by which capsaicin-sensitive afferents regulate vascular, secretory, motor, and emergency functions of the stomach, a region in which these functional implications have most thoroughly been investigated.

Innervation of the Stomach by Extrinsic Afferent Nerve Fibers

The extrinsic afferent nerve fibers supplying the stomach arise from two different sources (Figure 1). The spinal sensory neurons originate from cell bodies in the dorsal root ganglia and reach the stomach via the splanchnic and mesenteric nerves, whereas the afferent

Abbreviations used in this paper: GMBF, gastric mucosal blood flow; NK, neurokinin.

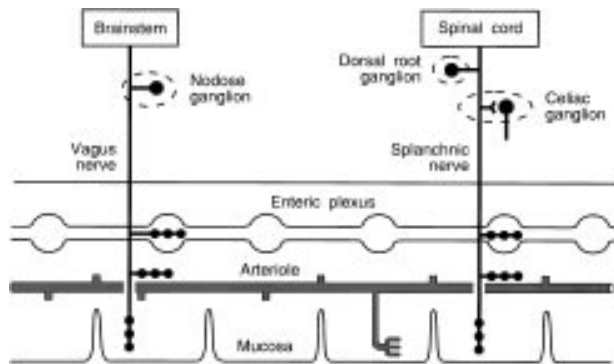


Figure 1. Innervation of the mammalian stomach by extrinsic primary afferent neurons. Afferent neurons in the vagus nerves originate from the nodose ganglia, whereas afferent neurons in the splanchnic nerves have their cell bodies in the dorsal root ganglia.

fibers in the vagus nerves have their cell bodies in the nodose and jugular ganglia.³ Typically, the spinal afferents contain a variety of bioactive peptides, including calcitonin gene-related peptide (CGRP) and the tachykinins substance P (SP) and neurokinin (NK) A.⁴⁻⁷ The chemical coding by CGRP and SP is characteristic of extrinsic afferent neurons, whereas intrinsic enteric neurons in the rodent and canine stomach do not coexpress these peptides.^{5,6} In addition, most of the CGRP present in afferent neurons is CGRP- α , whereas the only form of CGRP in enteric neurons is CGRP- β .^{6,7} Another difference is that only primary afferent neurons are sensitive to the excitotoxic action of capsaicin, whereas autonomic and enteric neurons are not. Thus, pretreatment of rats with a neurotoxic dose of capsaicin depletes afferent neuron-derived peptides from the stomach (Table 1), whereas messengers contained in autonomic and enteric neurons or in endocrine cells of the stomach (e.g., galanin, gastrin, histamine, 5-hydroxytryptamine, methionine enkephalin, neuropeptide Y, somatostatin, and vasoactive intestinal polypeptide) are left unchanged.^{2,4-6,8} With the help of capsaicin, it has been shown that the CGRP-containing nerve fibers in the rat stomach arise exclusively from extrinsic afferent neurons, whereas SP-

immunoreactive fibers are of both extrinsic and intrinsic origin (Table 1).^{4,6}

Most extrinsic nerve fibers expressing CGRP and SP in the rodent stomach are spinal rather than vagal afferents that, on their way from the dorsal root ganglia to the gut, pass through the prevertebral ganglia (Figure 1) where they give off collaterals to form synapses with sympathetic ganglion cells.^{4,9-11} Some studies, however, hold that vagal afferents expressing SP and CGRP supply the oxyntic part of the feline and rat stomach,^{9,12} whereas other studies negate such an innervation by vagal afferents.^{4,10} Most probably, this discrepancy reflects a decrease in the density of peptidergic vagal afferents from the proximal to the distal stomach because the gastric corpus of the cat is innervated by vagal SP-containing fibers, whereas the extrinsic supply of SP-positive fibers in the antrum, pylorus, and duodenum is derived from spinal afferents.⁹ Within the rodent gastric wall, it is particularly the arterial and arteriolar system that receives a dense supply by spinal afferent nerve fibers expressing CGRP, SP, and NKA (Figure 1), whereas the venous system is rather sparsely innervated.^{4,6,13} The peptide-containing axons run primarily in the connective tissue (adventitia) surrounding the vessels and at the border between adventitia and muscle (media). In addition, some peptide-containing afferent nerve fibers supply the myenteric plexus, the circular muscle layer, and the mucosa of the gut.^{4,6,10,12,13}

Physiological Implications of Extrinsic Afferents in the Stomach

Gastric Blood Flow

Vasodilation caused by afferent neuron stimulation. Stimulation of afferent nerve fibers by short-term intragastric administration of capsaicin causes a marked increase in gastric mucosal blood flow (GMBF; Table 2).¹⁴⁻¹⁸ This effect is brought about by dilation of submucosal arterioles, but not venules,¹⁷ and depends on the integrity of the extrinsic afferent innervation of the stomach, because pretreatment of rats with a neurotoxic dose of capsaicin prevents the hyperemic response to sensory neuron stimulation.¹⁵ Nerve-selective ablation of afferent nerve fibers has shown that only spinal afferent neurons passing through the celiac ganglion participate in the capsaicin-evoked increment of GMBF.¹⁶

CGRP and nitric oxide as mediators of neurogenic vasodilation. Because the capsaicin-evoked increase of rat GMBF does not involve cholinergic vasodilator neurons and noradrenergic neurons, it has been inferred that neurogenic hyperemia in the rat stomach is brought about by local release of vasodilator transmitters from

Table 1. Effect of Capsaicin-Induced Defunctionalization of Afferent Neurons on Neuropeptide Immunoreactivity in the Rat Stomach

Route of capsaicin administration	Messenger	Effect of capsaicin administration
Perivagal	CGRP	No change ⁸
Periceliac	CGRP	Loss from gastric corpus wall ⁸
Systemic	CGRP	Loss from gastric corpus wall ^{4-6,24,82,95,108,137}
	SP	Loss from blood vessels, submucosa, and mucosa but not from external muscle layer ⁴

Table 2. Functional Responses to Afferent Neuron Stimulation in the Stomach and Their Mediators

Function	Stimulus	Response	Mediators
Neuropeptide release			
CGRP release	Acid Capsaicin	Stimulation ^{24,60} Stimulation ^{22-25,108,146}	
SP/NKA release	Capsaicin	Stimulation ^{31-33,121}	
Motility			
LES pressure	Capsaicin	Increase	SP and NKA ⁷³
Gastric motor activity	Capsaicin	Stimulation Inhibition ⁷⁴⁻⁷⁶	SP and NKA ^{15,74-76}
Gastric emptying	Capsaicin Acid Abdominal surgery	Inhibition ^{77,78,110} Inhibition Inhibition	CGRP ⁸⁸ CGRP ^{140,141}
Exocrine and endocrine secretion			
Acid output	Capsaicin	No change ^{18,34,52,125,134,146} Inhibition	CGRP ^{58,59}
Bicarbonate and mucus output	Capsaicin	Stimulation ^{53,54}	
Pepsin output	Capsaicin	Inhibition ⁹¹	
Acetylcholine release	Capsaicin	Inhibition	CGRP ²⁵
Gastrin release	Acid Capsaicin	Inhibition Inhibition	CGRP ⁶⁰ CGRP ²⁵
Somatostatin release	Acid Capsaicin	Stimulation Stimulation	CGRP ⁶⁰ CGRP ^{23,25}
Vascular functions			
Mucosal blood flow	Capsaicin Acid CCK octapeptide Intracisternal TRH	Increase Increase Increase Increase	CGRP and NO ^{14-19,28,30,34,39} CGRP and NO ^{8,57,124-128} CGRP and NO ⁴⁶ CGRP ⁴⁵
Vascular permeability	Capsaicin	No change in rat ^{47-49,110} Increase in mouse ⁵⁰	

CCK, cholecystokinin; LES, lower esophageal sphincter; TRH, thyrotropin-releasing hormone.

perivascular afferent nerve fibers.^{14,15,19} The major transmitter appears to be CGRP (Table 2) because the CGRP₁ receptor antagonist CGRP₈₋₃₇ prevents the gastric vasodilation caused by capsaicin-evoked sensory neuron stimulation.^{16,17,19} However, it needs to be realized that the data obtained with CGRP₈₋₃₇ prove the implication of CGRP₁ receptors but not necessarily of CGRP itself. This is because peptides with some structural homology to CGRP, such as adrenomedullin and amylin, can also activate CGRP₁ receptors, and vasodilator responses to both amylin²⁰ and adrenomedullin²¹ are antagonized by CGRP₈₋₃₇. However, it is not known whether amylin and adrenomedullin are transmitters of gastric sensory neurons, whereas CGRP is readily released from the rat stomach when afferent nerve fibers are stimulated by capsaicin (Table 2).²²⁻²⁵ Exogenous CGRP is very active in increasing blood flow through the rat and rabbit stomach,^{16,26,27} an action that is mediated by CGRP₁ receptors.^{16,17} Like capsaicin, CGRP dilates submucosal arterioles but not venules, which is in keeping with the presence of CGRP receptors on arterial vessels of the rat stomach.⁶

The vasodilator action of exogenous and endogenous CGRP in the rat stomach involves the formation of NO (Table 2) because NO synthase inhibitors blunt the gastric hyperemic reaction to both capsaicin and

CGRP.^{19,28-30} The localization of CGRP receptors on the endothelium of gastric arterioles⁶ suggests that CGRP acts primarily on endothelial cells to stimulate the formation of NO, although some direct action on the vascular smooth muscle is also likely (Figure 2).²⁹ However, the actual sources of NO that are mobilized by

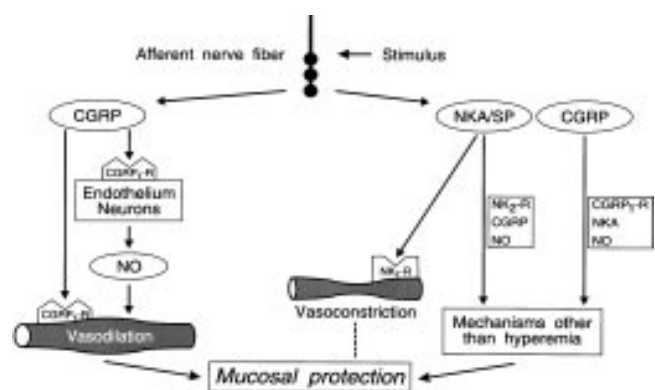


Figure 2. Summary of the vasodilator and protective mechanisms that, in the rat stomach, are initiated by stimulation of extrinsic afferent neurons and subsequent release of peptide transmitters. Whereas CGRP causes vasodilation, NKA and SP elicit vasoconstriction. Both CGRP and NKA/SP stimulate hyperemia-independent mechanisms of protection. The protective action of CGRP involves NKA and NO, whereas that of NKA/SP depends on CGRP and NO.³⁵ CGRP₁-R, CGRP₁ receptor; NK₁-R, tachykinin NK₁ receptor; NK₂-R, tachykinin NK₂ receptor.

sensory neuron stimulation and CGRP are not known. Discrepancies in the contribution of NO to the gastric vasodilator actions of capsaicin and CGRP³⁰ make it conceivable that sensory neuron stimulation releases NO not only from endothelial cells but also from extrinsic afferent and/or intrinsic enteric neurons. None of these possibilities, though, has been tested yet.

Although released by capsaicin from afferent nerve fibers,³¹⁻³³ SP and NKA do not mediate vasodilation in the rat stomach because the capsaicin-induced hyperemia is left unaltered by tachykinin NK₁ or NK₂ receptor antagonists^{34,35} and because tachykinins fail to dilate submucosal arterioles³³ and to augment GMBF.^{27,36} To the contrary, SP and NKA constrict rat gastric submucosal venules,³³ decrease rat GMBF,^{35,37} and reduce the capsaicin-induced hyperemia in the rat stomach through liberation of mast cell proteases.³⁶

Vasoactive mediators of mast cells such as histamine likewise do not contribute to the capsaicin-evoked increase of GMBF under normal circumstances,^{34,36,38} whereas the potential role of prostaglandins is unclear. Although capsaicin fails to alter the *ex vivo* formation of prostaglandin E₂, 6-oxo-prostaglandin F_{1 α} , and leukotriene C₄ in the rat gastric mucosa,¹⁴ the cyclooxygenase inhibitor indomethacin has been reported to diminish the capsaicin-induced increase in rat GMBF.^{34,39} Because the specificity of indomethacin in blocking prostaglandin synthesis has not been ascertained in these experiments, the participation of vasodilator prostaglandins remains ambiguous.

Physiological implications of afferent vasodilator nerve fibers in the stomach. Because pretreatment of rats with a neurotoxic dose of capsaicin does not change basal blood flow in the rat gastric corpus (Table 3),^{8,15,16,18,40} it seems that afferent vasodilator nerve fibers do not regulate GMBF under basal conditions. However, these neurons interact with other vascular control systems. Thus, ablation of capsaicin-sensitive afferent neurons attenuates the autoregulatory escape from epinephrine-induced vasoconstriction in the rat gastric mucosa,⁴¹ which implies that sympathetic vasoconstriction is counteracted by afferent neuron-mediated vasodilation. Analogously, the ability of NO synthase inhibitors to cause gastric vasoconstriction is amplified after capsaicin-induced ablation of afferent neurons.⁴² The interaction between tonically synthesized NO^{29,42} and stimulus-driven afferent nerve fibers suggests that these two systems act in concert to provide an active dilator drive on the gastric microcirculation.⁴³

Another interaction of physiological relevance concerns the possibility that vagal efferents can increase GMBF via stimulation of afferent vasodilator neurons. Electrical stimulation of the rat vagus nerves causes a

Table 3. Effect of Capsaicin-Induced Defunctionalization of Afferent Neurons on Vascular, Secretory, and Motor Functions of the Rat Stomach

Function	Effect of capsaicin pretreatment
Vascular functions	
Basal MBF	No change ^{8,15,16,34,40,41,44,45,57,106}
MBF increase caused by acid backdiffusion	Inhibition by systemic and periceliac capsaicin ^{8,17,57,92,124,125}
Increase in MBF caused by capsaicin	No change by perivagal capsaicin ⁸ Inhibition by systemic and periceliac capsaicin ^{15,16,34,106,125} No change by perivagal capsaicin ¹⁶
MBF increase caused by CCK octapeptide	Inhibition ⁴⁶
Escape from epinephrine vasoconstriction	Inhibition ⁴¹
Secretory functions	
Basal acid and pepsin output	No change ^{18,34,44,61-67,89,106}
Basal bicarbonate and pepsin output	No change ^{53,56}
Basal mucus output	No change in gastric corpus but increase in antrum ⁴⁰
Acid output caused by vagal nerve stimulation	No change by systemic capsaicin ⁶² Inhibition by perivagal capsaicin ⁶⁵
Acid output caused by histamine	No change by systemic capsaicin ^{63,106} Inhibition by perivagal capsaicin ⁶¹
Acid output caused by pentagastrin	No change ^{61,63,64,67}
Acid output caused by peptone	Inhibition ⁶³
Acid output caused by gastric distention	Inhibition ^{61,62}
Acid-stimulated bicarbonate output	Inhibition ⁵³
Motor functions	
Basal motor activity and emptying	No change ^{76,81-87,137-139,142}
Motor activation by vagal nerve stimulation	No change ⁸⁶
Motor inhibition by celiac ganglion stimulation	No change ⁸¹
Motor inhibition by intragastric acid or peptone	Attenuation ⁸²
Motor inhibition by intraduodenal acid	Attenuation ^{81,83}
Motor inhibition by intraduodenal lipid	Attenuation by perivagal capsaicin ⁸⁵ No change by periceliac capsaicin ⁸⁵
Motor inhibition by intraduodenal glucose	Attenuation ⁸⁴
Motor inhibition by CCK or secretin	Attenuation ^{86,87}
Motor inhibition by duodenal distention	Attenuation ⁸⁰
Motor inhibition by peritoneal irritation	Attenuation ¹³⁷⁻¹³⁹
Motor inhibition by abdominal surgery	Attenuation by systemic and periceliac capsaicin ^{137,139-142} No change by perivagal capsaicin ^{140,142}

CCK, cholecystokinin; MBF, mucosal blood flow; periceliac, local treatment of the celiac ganglion with capsaicin to ablate spinal afferents from the stomach; perivagal, perivagal application of capsaicin to ablate vagal afferents from the stomach.

noncholinergic increase of GMBF that involves capsaicin-sensitive afferent neurons.⁴⁴ In some way, this effect resembles the gastric hyperemic response to intracisternal thyrotropin-releasing hormone, which is inhibited by atropine, ablation of capsaicin-sensitive afferent neurons, and CGRP₈₋₃₇.⁴⁵ Because the gastric vasodilation evoked by muscarinic acetylcholine receptor stimulation is also inhibited by the CGRP receptor antagonist,⁴⁵ it is inferred that CGRP comes into play secondarily to acetylcholine and that, hence, afferent vasodilator neurons mediate the hyperemic effect of efferent vagal nerve stimulation. A similar pathway involving acetylcholine and CGRP underlies the gastric vasodilator response to intravenous cholecystokinin octapeptide.⁴⁶ The interface between parasympathetic efferent neurons and CGRP-releasing afferent nerve fibers remains to be elucidated.

Vascular Permeability in the Stomach

A distinct response to afferent neuron stimulation in many tissues is an increase in venular permeability, a reaction that facilitates the extravasation of macromolecules, leukocytes, and fluid.⁵ In the rat stomach, however, no consistent increase in the leakage of Evans blue-labeled plasma albumin is observed after capsaicin-induced stimulation of afferent nerve fibers (Table 2).⁴⁷⁻⁴⁹ In contrast, capsaicin causes appreciable plasma protein extravasation in the stomach of the mouse (Table 2), which is mediated by SP and/or NKA because it is blocked by an NK₁ receptor antagonist.⁵⁰ The species-dependent effect of capsaicin on vascular permeability is mirrored by a species-dependent action of exogenous tachykinins. Thus, SP stimulates plasma extravasation in the murine stomach via activation of NK₁ receptors,⁵⁰ whereas in the rat stomach, SP and NKA fail to induce consistent and significant leakage of plasma proteins.^{48,51} Whether peptides released from afferent nerve fibers affect leukocyte recruitment in the stomach has not been tested yet.

Gastric Secretion

Physiological impact of afferent neurons on basal gastric secretion. Capsaicin-evoked stimulation of gastric afferent nerve fibers does not significantly alter the basal secretion of acid in the rat and canine stomach, whereas the elimination of acid from the gastric lumen is increased^{18,34,52} as a result of enhanced GMBF,¹⁴⁻¹⁶ enhanced bicarbonate secretion,⁵³ and enhanced mucus output (Table 2).⁵⁴ Only under the pathological conditions of pylorus ligation in conscious rats has capsaicin been found to reduce basal gastric acid output and to blunt the secretory responses to bethanechol, pentagastrin, and histamine.⁵⁵

Defunctionalization of capsaicin-sensitive afferent neurons likewise fails to change the basal secretion of gastric acid, pepsin, and bicarbonate and does not alter the permeability of the gastric mucosa to acid and ions (Table 3).^{18,34,44,53,56,57} The basal secretion of mucus in the rat gastric corpus remains unaltered, whereas that in the antrum is reduced (Table 3).⁴⁰ It therefore appears that capsaicin-sensitive afferents do not take any significant part in the regulation of basal gastric secretion, although it needs to be considered that chronic ablation of afferent neurons triggers compensatory mechanisms that balance the missing input from afferent neurons. This conjecture is supported by the observation that basal acid secretion is enhanced and the secretory response to pylorus ligation, pentagastrin, and bombesin is facilitated when the action of CGRP released from afferent nerve fibers is prevented acutely by CGRP₈₋₃₇ or a monoclonal CGRP antibody.^{58,59}

Physiological impact of afferent neurons on stimulated gastric secretion. Capsaicin-sensitive afferents can be dissociated into two groups that regulate gastric secretion by two distinct mechanisms of action (Figure 3). One group of afferent nerve fibers in the gastric mucosa responds to luminal acidification and represents a negative feedback system in gastric secretory control (Figure 3).⁶⁰ Thus, accumulation of acid in the gastric lumen releases CGRP, which acts on CGRP₁ receptors, to facilitate the release of somatostatin and to depress the release of gastrin and, in this way, inhibits further acid output.^{24,59,60} It is not yet known whether capsaicin-sensitive afferents mediate acid-evoked output of gastric bicarbonate (Table 3)⁵³ via a similar mechanism of action.

Another group of capsaicin-sensitive afferent neurons constitutes the afferent arc of autonomic secretory and antisecretory reflexes (Figure 3). Thus, acid secretion

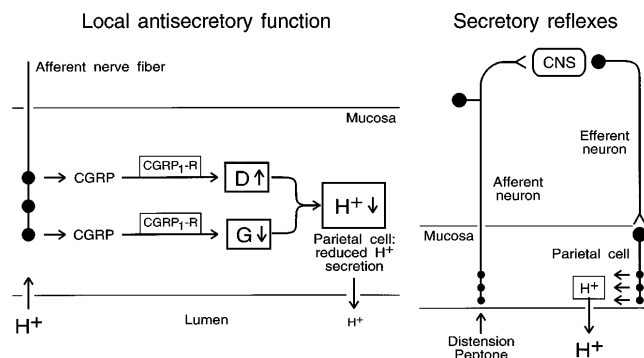


Figure 3. Diagram showing two groups of extrinsic afferent neurons that regulate gastric acid secretion in the rat stomach via two distinct mechanisms. Acid-sensitive nerve fibers in the gastric mucosa release CGRP and thereby inhibit acid secretion, whereas other fibers that are sensitive to distention or peptone constitute the afferent arc of secretory reflexes. CGRP₁-R, CGRP₁ receptor; CNS, central nervous system; D, gastric D (somatostatin) cells; G, gastric G (gastrin) cells.

elicited by gastric distention^{61,62} or peptone⁶³ is attenuated after capsaicin-induced ablation of sensory neurons. Capsaicin-sensitive afferents may also contribute to secretagogue-evoked acid secretion; however, because of discrepancies in the reports, it is presently not possible to draw an integrated hypothesis as to how stimulation of gastric secretion by gastrin, histamine, and vagal nerve stimulation depends on afferent neurons (Table 3).^{44,61,64,65} Finally, afferent neurons control enterogastric inhibition of acid secretion because capsaicin-induced ablation of sensory neurons prevents intraduodenal lipid⁶⁶ and acid⁶⁷ from suppressing gastric acid secretion. Although the secretory response to gastric distention^{61,62} and the enterogastric inhibition of gastric secretion caused by intraduodenal acid⁶⁷ involve both vagal and splanchnic afferents, it is only vagal afferents⁶⁶ that mediate the inhibitory effect of intraduodenal lipid on gastric acid secretion (Table 3).

Mediators by which afferent neurons control gastric secretion. CGRP appears to be the major transmitter by which afferent nerve fibers within the gastric mucosa suppress acid output (Figure 3 and Table 2). This inference is in keeping with the peptide's high activity to inhibit acid secretion in the rat and canine stomach via activation of CGRP₁ receptors.^{58,59,68} The antisecretory action of CGRP involves release of somatostatin, whereas the release of gastrin and acetylcholine is attenuated (Table 2),^{23,25,60} as is the release of histamine from enterochromaffin-like cells.⁶⁹ An involvement of tachykinins in afferent neuron-mediated changes of gastric secretion has not been tested yet, although such an implication is conceivable given that tachykinins have species-dependent effects on gastric exocrine and endocrine secretion⁷⁰ and, in the rat stomach, can inhibit the release of somatostatin via activation of NK₂ receptors on D cells.⁷¹ Pituitary adenylate cyclase-activating peptide is a peptide that suppresses basal and stimulated acid secretion in the rat stomach via a direct action on parietal cells,⁷² but it remains to be examined whether pituitary adenylate cyclase-activating peptide participates in afferent neuron-mediated control of gastric acid output.

Gastric Motor Activity

Motor responses to afferent neuron stimulation and their mediators. Stimulation of extrinsic sensory neurons exerts both stimulant and inhibitory effects on gastric motor activity. Local administration of capsaicin enhances the lower esophageal sphincter pressure in the dog via a pathway that involves cholinergic motor neurons (Table 2).⁷³ The rat stomach responds to short-term administration of capsaicin with both contraction and relaxation, the type of response depending on the

dose of capsaicin and the gastric region and muscle layer under study.^{15,74-76} These composite motor changes result in inhibition of gastric propulsion and emptying (Table 2), an effect that chili and capsaicin induce in both rats and humans.^{77,78} The muscle relaxation caused by capsaicin in the rat stomach depends on extrinsic afferent neurons⁷⁴ but does not involve SP or CGRP.⁷⁴⁻⁷⁶ Tachykinins, however, contribute to the capsaicin-induced contraction of the rat stomach (Table 2)⁷⁵ and canine lower esophageal sphincter.⁷³ The tachykinin-mediated contraction that splanchnic nerve stimulation elicits in the canine stomach is thought to arise from antidromic activation of extrinsic afferent neurons, which stimulate cholinergic motor neurons through peripheral transmitter release.⁷⁹

Physiological implications of afferent neurons in gastric motor control. Basal gastric motor activity and basal gastric emptying are not altered in rats pretreated with a neurotoxic dose of capsaicin.^{76,80-82} However, capsaicin-sensitive afferents participate in inhibitory gastric motor reflexes evoked by duodenal distention,⁸⁰ intragastric or intraduodenal administration of acid,⁸¹⁻⁸³ intraduodenal administration of nutrients (e.g., peptone, glucose, or lipid),^{84,85} or intravascular administration of cholecystokinin or secretin (Table 3).^{86,87} Analysis of the underlying pathways has shown that the inhibitory motor response to cholecystokinin, secretin, or intraduodenal lipid is mediated by vagal nerve fibers⁸⁵⁻⁸⁷ that form the afferent arc of the inhibitory motor reflexes. In contrast, the gastroparesis caused by intrajejunal acid depends on spinal afferents that send axon collaterals into the celiac ganglion^{4,9-11} where they stimulate sympathetic output and thus inhibit gastric motor activity via a short-loop sympathetic reflex (Table 3).⁸⁰ The mechanism by which intragastric acid inhibits gastric emptying involves CGRP as a transmitter substance (Table 2).⁸⁸

Pathophysiological Implications of Extrinsic Afferents in the Stomach

Gastric Mucosal Resistance to Injury

Enhancement of gastric mucosal vulnerability by sensory neuron ablation. The ability of sensory neurons to strengthen gastric mucosal resistance to damage was first envisaged when Szolcsányi and Barthó⁵⁶ discovered that capsaicin-induced ablation of afferent neurons aggravated gastric injury caused by pylorus ligation. Subsequent studies have proved that pretreatment of rats with a neurotoxic dose of capsaicin does not cause damage by itself^{40,47,89-91} but exacerbates mucosal lesion formation caused by injurious factors such as water immersion restraint stress,⁹¹ hydrochloric acid,^{8,56,57} tau-

rocholate,⁹² platelet-activating factor,⁹³ endothelin 1,⁹⁴ acetic acid,⁹⁵ acetylsalicylic acid (aspirin),^{90,91} indomethacin,^{89,90,96} and ethanol.^{40,89-91} The gastroprotective potential of sensory neurons is further underlined by the observation that capsaicin-induced ablation of afferent neurons compromises the ability of many factors and drugs to protect the gastric mucosa from injury.⁹⁷⁻¹⁰³ For instance, gastroprotection afforded by cholecystokinin octapeptide, gastrin 17, the antiulcer drug ecabet, the antacid hydrotalcit, the proton pump inhibitor lansoprazole, and prostaglandin E₂ is reduced or abolished in capsaicin-pretreated rats (Table 4). Gastric mucosal adaptation to water immersion restraint stress is also prevented by capsaicin pretreatment,⁹¹ whereas adaptive cytoprotection caused by mild irritants such as dilute ethanol, HCl, or NaOH is either attenuated¹⁰⁴ or left unchanged.¹⁰⁵

Gastric mucosal protection afforded by sensory neuron stimulation. The evidence for a gastroprotective role of sensory neurons, as deduced from the deleterious effect of capsaicin-induced ablation of extrinsic afferents, is complemented by the observation that capsaicin-induced stimulation of afferents enhances gastric mucosal resistance to injury (Table 4). Short-term intragastric administration of capsaicin protects the rat and canine stomach from a wide spectrum of injurious factors, which, among others, include hydrochloric acid,^{52,56,106} acidified taurocholate,^{19,52} aspirin,^{91,107} indomethacin,¹⁰⁸ and ethanol.^{14,15,39,47,54,76,91,109} The protective effect of

capsaicin manifests itself in a reduction of the depth and extent of mucosal injury, whereas surface damage is not prevented.^{14,15,54,107,109} In contradiction of traditional views, intragastric administration of capsaicin does not irritate the gastric mucosa and does not in any way weaken the gastric mucosal barrier, as has been assumed for some red pepper spices that contain many substances other than capsaicin. Capsaicin fails to enhance back-diffusion of gastric acid, does not appreciably enhance vascular permeability in the gastric wall, leaves the transmucosal potential difference unchanged, and fails to cause any macroscopic or histological damage by its own.^{18,34,47,52,107,110} It can be ruled out, therefore, that capsaicin strengthens gastric mucosal resistance to injury by virtue of an irritant action on the mucosa.

The beneficial action of purified capsaicin on gastric mucosal homeostasis is shared by chili powder, which contains a large amount of capsaicin and thereby protects the rat gastric mucosa from ethanol injury.⁵⁴ It is of particular importance to note that the gastroprotective effect of chili is reproduced in humans. Thus, ingestion of 20 g chili powder fails to cause any injury of the human gastroduodenal mucosa as assessed by endoscopy and biopsy but reduces the mucosal damage caused by 600 mg aspirin.¹¹¹ Furthermore, there is epidemiological evidence that dietary chili ingestion has a protective action against peptic ulcer disease because within the multiracial population of Singapore the frequency of ulcer disease correlates inversely with the amount of chili intake.¹¹²

Pathways of sensory neuron-mediated gastric mucosal protection. The gastroprotective effect of capsaicin depends on an intact sensory innervation of the stomach because it is blunted by capsaicin-induced ablation of extrinsic afferent neurons.^{15,47,108} An implication of neurons is also deduced from the finding that nerve conduction blockade with tetrodotoxin¹⁵ or lidocaine¹¹³ attenuates the ability of capsaicin to prevent ethanol injury, although the underlying neural pathways have not been delineated yet. Because acute vagotomy, acute extirpation of the celiac ganglion, and acute ligation of the blood vessels to the adrenal glands do not compromise the gastroprotective action of capsaicin, it is inferred that sensory neuron stimulation strengthens gastric mucosal resistance to injury via local release of transmitters within the gastric wall.^{14,15,47} As is the case with neurogenic vasodilation,^{45,46} the action of afferent nerve fibers in promoting gastric mucosal defense can be stimulated by vagal efferents. Thus, intracisternally administered thyrotropin-releasing hormone activates cholinergic efferent neurons in the vagus nerve, which in turn cause capsaicin-sensitive afferents to release CGRP

Table 4. Implication of Capsaicin-Sensitive Afferent Neurons and Their Mediators in the Effects of Protective Drugs in the Rat Stomach

Protective drug	Effect of capsaicin pretreatment	Mediators
Capsaicin	Abolition of protective effect ^{15,35,47,108,109,114}	CGRP ^{19,35,108,109,114} NKA ³⁵ NO ^{19,35,39,109}
CCK octapeptide	Inhibition of protective effect ⁹⁷	
Ecabet	Inhibition of protective effect ⁹⁹	NO ⁹⁹
<i>Escherichia coli</i> endotoxin	Inhibition of protective effect ¹⁰³	NO ¹⁰³
Gastrin 17	Inhibition of protective effect ⁹⁸	CGRP ⁹⁸ NO ⁹⁸
Hydrotalcit	Inhibition of protective effect ¹⁰⁰	NO ¹⁰⁰
Lansoprazole	Inhibition of protective effect ¹⁰¹	NO ¹⁰¹
NKA ₄₋₁₀	Inhibition of protective effect ³⁵	CGRP ³⁵ NO ³⁵
Prostaglandin E ₂	Inhibition of protective effect ¹⁰²	
Intracisternal TRH	Inhibition of protective effect ¹¹⁴	CGRP ¹¹⁴

CCK, cholecystokinin; TRH, thyrotropin-releasing hormone.

and thereby to render the gastric mucosa resistant to experimental injury.¹¹⁴

CGRP, tachykinins, and NO as mediators of sensory neuron-mediated gastric mucosal protection. There is conclusive evidence that gastric mucosal protection caused by afferent neuron stimulation is mediated by nonadrenergic, noncholinergic transmitters,⁴⁷ among which CGRP plays a central role (Figure 2 and Table 4). Thus, blockade of CGRP₁ receptors with CGRP₈₋₃₇^{19,109} or immunoneutralization of CGRP¹⁰⁹ prevents capsaicin from protecting the gastric mucosa, whereas active immunization of rats against CGRP exacerbates mucosal vulnerability to ethanol.¹¹⁵ The prominent role that CGRP plays in neurogenic gastroprotection is in keeping with the ability of exogenous CGRP to counteract gastric mucosal damage caused by ethanol and other injurious factors via activation of CGRP₁ receptors.^{68,94,108,109,116-118}

The gastroprotective action of capsaicin depends on NO (Table 4) because it is suppressed by NO synthase inhibitors.^{19,39,109} Because the ability of CGRP to strengthen gastric mucosal defense is likewise blocked by NO synthase inhibitors,^{109,118} it is inferred that sensory neuron stimulation by capsaicin results in release of CGRP, which augments the resistance of the gastric mucosa against experimental injury via formation of NO (Figure 2). Such a role of NO is consistent with its ability to prevent gastric mucosal injury and with the effect of NO synthase inhibitors to enhance gastric mucosal vulnerability in capsaicin-pretreated but not normal rats.^{43,96} The source of NO involved in the actions of capsaicin and CGRP has not been identified yet.

Tachykinins are not only released from extrinsic afferents in the stomach³¹⁻³³ but are also involved in sensory neuron-mediated defense of gastric mucosal integrity (Figure 2 and Table 4). This inference derives from the ability of the nepepudin-like NK₂ receptor antagonist MEN-10,627 to attenuate the gastroprotective action of capsaicin against ethanol injury.³⁵ It is in keeping with a mediator role that NKA and related NK₂ receptor agonists inhibit ethanol-induced lesion formation in the rat stomach via an action involving NO.^{35,119} In contrast, tachykinins acting preferentially via NK₁ receptors impair mucosal homeostasis because SP exaggerates gastric mucosal damage caused by acidified taurocholate or ethanol.¹²⁰ The deleterious effect of SP involves mast cell degranulation and subsequent release of histamine and other autacoids that have an adverse effect on gastric mucosal integrity.¹²⁰ Endogenous tachykinins share this adverse action of exogenous SP because ethanol releases SP into the gastric lumen, SP constricts mucosal and submucosal venules, and tachykinin antagonists reduce ethanol-induced injury.^{33,120,121}

Taken together, the data indicate that both CGRP

acting via CGRP₁ receptors and tachykinins acting via NK₂ receptors are transmitters of extrinsic afferent neurons that govern gastric mucosal defense against injury. Both transmitters use NO as a second messenger. In addition, the gastroprotective effect of NK₂ receptor agonists depends on an intact sensory innervation of the stomach and involves release of CGRP,³⁵ which implies that tachykinins interact with CGRP in their action on gastric mucosal integrity (Figure 2). It is also noteworthy that transmitter release from sensory nerve fibers is under the inhibitory control of opiate receptors.⁵ Because the ability of morphine to aggravate gastric damage is lost after capsaicin-induced ablation of afferent neurons,^{93,102,122} it appears as if morphine weakens gastric mucosal resistance to injury by inhibiting the gastroprotective action of capsaicin-sensitive afferents.

The evidence to implicate prostaglandins as mediators of sensory neuron-mediated gastric mucosal protection is controversial. Intragastric capsaicin does not affect the *ex vivo* formation of prostaglandin E₂, 6-oxo-prostaglandin F_{1α}, and leukotriene C₄, and indomethacin fails to alter the protective effect of capsaicin.¹⁴ The ability of CGRP to enhance the resistance of the gastric mucosa to injury remains likewise unaltered by indomethacin.¹⁰⁹ Some investigators, however, have found that the gastroprotective action of capsaicin is reduced by indomethacin,^{39,76,110,113} but it has not been ascertained in these studies whether the effect of indomethacin is in fact caused by inhibition of prostaglandin synthesis.

Hyperemia as a mechanism of sensory neuron-mediated gastric mucosal protection. The identity of CGRP and NO as messengers of both the hyperemic and protective response to afferent neuron stimulation and the remarkable correlation between these two reactions^{15,39} point to a close relationship between the increase in GMBF and the increase in mucosal resistance to injury. However, this parallelism does not prove that hyperemia is the primary mechanism by which afferent neuron stimulation strengthens gastric mucosal defense. Evidence is in fact accumulating that protective mechanisms other than vasodilation are also operated by afferent nerve fibers, although hyperemia is likely to support a wide range of defensive forces in the gastric mucosa (Figure 4). This support role of hyperemia is particularly important for an appropriate output of gastric bicarbonate that is stimulated by sensory neuron stimulation⁵³ and that depends on an adequate blood flow to deliver bicarbonate to the surface mucus layer.¹

Hyperemia-independent mechanisms of sensory neuron-mediated gastric mucosal protection. A major hint that mechanisms other than an increase of GMBF contribute to afferent neuron-mediated defense of

Mediators	Mechanisms	
CGRP (CGRP ₁ -R) NKA, SP (NK ₂ -R) NO	<i>Hyperemia</i>	<i>Hyperemia-independent mechanisms</i>
	<i>Hyperemia-dependent mechanisms</i>	Endothelial protection
	Bicarbonate secretion	Mucus secretion
	<i>Hyperemia-facilitated mechanisms</i>	Luminal dilution
	Restitution	Reduction of acid output
	Healing	Reduction of gastric emptying
		Trophic effects

Figure 4. Summary of the mediators and presumed mechanisms by which afferent neuron stimulation enhances the resistance of the stomach to injury. CGRP₁-R, CGRP₁ receptor; NK₂-R, tachykinin NK₂ receptor.

gastric injury has come from studies with the nepeptide-like NK₂ receptor antagonist MEN-10,627, which attenuates the gastroprotective action of capsaicin but fails to inhibit the concomitant hyperemia.³⁵ This observation is in keeping with the ability of NKA-related peptides to enhance gastric mucosal resistance to experimental injury, despite a marked reduction of GMBF,³⁵ and implies that the component of afferent neuron-mediated gastroprotection that involves endogenous tachykinins acting via NK₂ receptors is independent of gastric mucosal hyperemia. Further evidence for a dissociation between the antileision and vasodilator activity of sensory neuron stimulation is provided by the local anesthetic lidocaine that blocks the hyperemic response to capsaicin in the canine gastric mucosa but fails to prevent capsaicin from reducing experimental damage.⁵² Conversely, pretreatment of rats with a neurotoxic dose of capsaicin exacerbates mucosal damage caused by hypertonic saline but fails to abrogate the concurrent gastric vasodilation.¹²³ Finally, CGRP counteracts the injurious influence of endothelin 1 and, at the same time, inhibits the hyperemic response to endothelin 1 in the rat gastric mucosa,¹¹⁷ which suggests that CGRP enhances gastric mucosal resistance by protecting the vascular endothelium from injury rather than by causing vasodilation.¹¹⁷

The nature of the hyperemia-independent gastroprotective mechanisms that are operated by capsaicin-sensitive afferent neurons has not been identified yet with certainty, although many possibilities have been envisaged (Figure 4). Inhibition of gastric emptying together with a possible increase in fluid secretion may result in dilution of the injurious factors in the gastric juice (Figure 4) and, thus, afford protection of the gastric mucosa.¹¹⁰ Whether the ability of sensory neuron stimulation to modulate gastric acid secretion (Figure 3 and Table 2) has any bearing on gastroprotection is not known. It seems more likely that the capsaicin-induced attenuation of acid output^{55,91} reflects increased bicarbonate secretion⁵³ and acid elimination¹⁸ rather than reduced acid secretion.

Another protective mechanism is reflected by the ability of capsaicin to stimulate the secretion of gastric mucus.⁵⁴

Gastric Vasodilation Evoked by Acid Backdiffusion

Participation of sensory neurons in the acid-evoked gastric hyperemia. The function of extrinsic afferent neurons in the regulation of gastric blood flow and mucosal resistance to injury is put into pathophysiological perspective if their role in the gastric response to acid challenge is considered. Disruption of the gastric mucosal barrier by ethanol^{57,124} or taurocholate^{19,92} in the presence of luminal acid causes backdiffusion of acid into the mucosa and a prompt increase of blood flow through the left gastric artery and gastric mucosa. The rapid signaling between the acid-threatened mucosal surface and submucosal resistance vessels is performed by sensory neurons because the acid-evoked increase of gastric blood flow is inhibited by tetrodotoxin or pretreatment of rats with a neurotoxic dose of capsaicin.^{57,92,106,123-125} The sustained increase of GMBF that sequential exposure to hypertonic saline and acid elicits in the rat gastric mucosa is also mediated by capsaicin-sensitive afferents.¹²³ Further analysis has shown that the afferents responding to acid backdiffusion pass through the celiac ganglion and hence originate from spinal ganglia.⁸

Mediators and mechanisms of the acid-evoked gastric hyperemia. The vasodilator response to acid backdiffusion in the rat stomach depends on CGRP or a related peptide acting via CGRP₁ receptors because the CGRP₁ receptor antagonist CGRP₈₋₃₇ depresses the acid-evoked increase of blood flow after disruption of the mucosal barrier with ethanol^{124,126} or taurocholate.¹⁹ As is the case with the vasodilator response to exogenous CGRP,²⁸⁻³⁰ the acid-evoked hyperemia is blocked by NO synthase inhibitors in an enantiomer-selective manner.^{124,127} These data indicate that the increase of GMBF in response to acid backdiffusion is mediated by release of CGRP from extrinsic afferent nerve fibers, with CGRP in turn stimulating the formation of NO that acts as the final vasodilator messenger (Figure 5). It follows that CGRP and NO are the common mediators of the acid- and capsaicin-induced vasodilation in the rat stomach. In contrast, CGRP seems to play little role in the hyperemia that exposure to hypertonic saline in acid elicits in the feline stomach.¹²⁸ Thus, although the gastric vasodilator response to acid backdiffusion is conserved across different species, the mediators responsible for the increase of GMBF may be subject to considerable variation.

Although exogenous SP and NKA inhibit the acid-evoked increase of GMBF via activation of NK₂ receptors, it appears that endogenous tachykinins do not play a

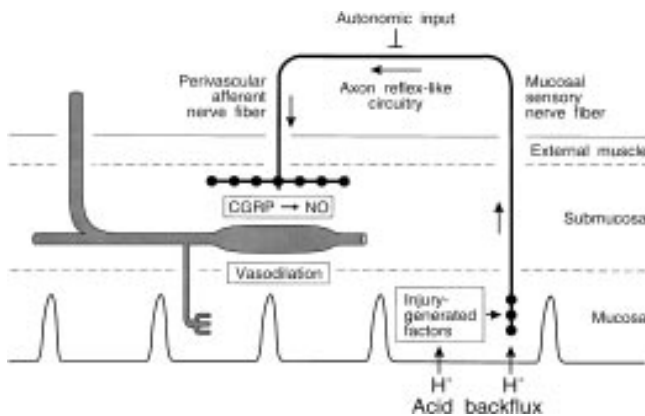


Figure 5. Diagram showing the pathways and mediators of the hyperemic response to acid backdiffusion in the rat stomach. Vasodilation is brought about by an axon reflex-like circuitry that is under the control of autonomic neurons in the splanchnic nerves.

significant role because NK₁ and NK₂ receptor antagonists fail to significantly alter the hyperemic response to acid backdiffusion in the rat.^{37,124} Histamine acting via histamine H₁ receptors,⁵⁷ vasodilator prostanoids,¹²⁷ acetylcholine acting via muscarinic receptors,⁵⁷ and transmitters of noradrenergic neurons¹²⁹ have likewise been ruled out as mediators of the acid-induced vasodilation in the rat stomach. Bradykinin, however, plays some role because the bradykinin B₂ receptor antagonist HOE-140 (icatibant) attenuates the hyperemia elicited by barrier disruption in the presence of a high concentration of intraluminal acid.¹³⁰ It therefore seems that amounts of bradykinin sufficient to increase GMBF are formed only during severe acid challenge of the gastric mucosa,¹³⁰ but it is not known whether bradykinin causes vasodilation on its own or by stimulating the neural vasodilator system.

The neural pathways, relays, and mechanisms that underlie the gastric hyperemic response to acid backdiffusion await to be elucidated in full detail. Because sympathetic noradrenergic neurons¹²⁹ and postganglionic parasympathetic or enteric cholinergic neurons⁵⁷ do not participate, it has been postulated that the acid-induced vasodilation results from an axon reflex between mucosal and submucosal collaterals of afferent neurons.^{5,57,126} It is in keeping with this theory that gastric acid challenge induces a calcium-dependent release of CGRP^{24,60} and that afferent neuron-derived CGRP is the major mediator of the acid-evoked hyperemia.^{124,126} However, the increase of gastric blood flow also depends on intact pathways in the splanchnic nerves and through the celiac ganglion^{129,131} and is inhibited by the autonomic ganglion blocking drug hexamethonium,^{129,131} which is difficult to reconcile with the axon reflex concept. In view of these discrepancies, it is hypothesized that the acid-induced increase in GMBF is relayed by a peripheral axon

reflex-like circuitry (Figure 5) that depends on an excitatory or inhibitory input from autonomic neurons in the splanchnic nerves.⁵ Whether this circuitry is directly stimulated by influxing acid or indirectly activated by factors that like bradykinin¹³⁰ are generated in the acid-threatened gastric mucosa has not been determined yet.

Gastric hyperemia in response to acid backdiffusion is aided by a reduction of blood flow to somatic vascular beds such as that of the femoral artery.¹³¹ However, the two reactions represent different entities with regard to pathways, mechanisms, and mediators. Thus, the femoral constrictor response to gastric acid challenge is a function of gastric injury because the gastric hyperemic response to capsaicin, which does not damage the gastric mucosa, is not accompanied by a reduction of femoral blood flow.¹³¹ With regard to the pathways, it has been found out that the gastric acid-evoked constriction of the femoral artery is independent of capsaicin-sensitive afferents, autonomic ganglionic transmission, noradrenergic neurons, or factors from the adrenal glands but requires an intact extrinsic innervation of the stomach,¹³¹ whereas the vasoconstrictor mediators remain to be identified.

Physiological relevance of the acid-evoked gastric hyperemia. Inhibition of the hyperemic response to gastric acid backdiffusion by tetrodotoxin,⁵⁷ capsaicin pretreatment,⁵⁷ morphine,⁵⁷ CGRP₈₋₃₇,¹²⁶ the bradykinin antagonist HOE-140 (icatibant),¹³⁰ or tachykinins³⁷ is associated with aggravation of gross and histological damage to the mucosa, which attests to the defensive nature of the blood flow reaction. By facilitating the disposal of acid, this mechanism prevents the build-up of an injurious concentration of H⁺ ions in the tissue and, thus, limits acid damage to the surface of the mucosa.^{1,57} It appears likely that the acid-induced secretion of gastric bicarbonate, which depends on an intact sensory innervation of the stomach,⁵³ is also largely a result of the acid-induced hyperemia. The afferent neuron-mediated vasodilator response to acid challenge reflects, therefore, the existence of a neural emergency system that is called into operation when there is pending or actual acid injury to the stomach.

Facilitation of Restitution and Healing

There is mounting evidence that not only acute defense against pending injury but also repair of the injured gastric mucosa is facilitated by sensory neurons. The process of restitution, which quickly restores the integrity of the superficial epithelium by mucous cell migration over denuded areas of the lamina propria, is per se independent of afferent neurons because restitution of the ethanol-injured gastric mucosa in the absence of luminal acid remains unchanged in rats pretreated with a

neurotoxic dose of capsaicin.¹³² Restitution, however, is accelerated by the afferent neuron-dependent vasodilation that is caused by acid backdiffusion after exposure of the rat stomach to hypertonic saline plus acid.¹²³ The sustained hyperemia that afferent neurons trigger in response to luminal acid also creates favorable conditions for proper healing of the wounded mucosa.¹⁰⁶ In addition, sensory neurons seem to promote genuine mechanisms of healing, given that the rate of repair of gastric ulcers induced by hydrochloric acid, acetic acid, or ethanol is delayed after sensory neuron ablation.^{95,106,133} The retarded healing of gastric corpus lesions observed in capsaicin-pretreated rats is associated with increased invasion of leukocytes into the gastric wall and with the development of antral ulcers.^{40,106,133}

In keeping with a role of afferent neurons in gastric mucosal healing is the observation that sensory neuron stimulation with low-dose capsaicin facilitates the healing of acetic acid-induced ulcers in the rat stomach.¹³⁴ Although the precise mechanisms of afferent neuron-promoted healing remain to be determined, it is relevant to keep in mind that the sensory neuron-derived peptides CGRP, SP, and NKA are able to stimulate the proliferation of fibroblasts and vascular smooth muscle and endothelial cells.^{5,70} Indirect evidence suggests that afferent nerve fibers may also exert a trophic influence on gastric mucosal cells (Figure 4). Thus, long-term intake of chili at doses that are expected to stimulate sensory nerve fibers in the rat stomach enhances gastric mucosal mass but does not change crypt cell proliferation or experimental carcinogenesis.¹³⁵ Conversely, ablation of capsaicin-sensitive afferent neurons reduces the weight of the stomach, the gastric synthesis of DNA, and the gastric content of DNA and RNA.¹³⁶

Pathological Inhibition of Gastric Motor Activity

Capsaicin-sensitive afferents contribute to the acute gastric motor inhibition that intragastric, intraduodenal, or intraperitoneal administration of acid, bradykinin and capsaicin,^{81-83,137,138} or abdominal surgery¹³⁹⁻¹⁴² elicit in the rat (Table 3). These inhibitory motor effects are in part relayed by a neural reflex that consists of capsaicin-sensitive afferent and sympathetic efferent neurons^{81,137-139} and whose pathways run through the celiac ganglion but not in the vagus nerves.^{81,140-142} Although the way by which abdominal surgery stimulates afferent neurons is little known, interleukin 1 β is thought to be a contributory factor because the inhibition of gastric emptying observed after abdominal surgery is attenuated by an interleukin 1 β receptor antagonist.¹⁴³ The inhibitory action of abdominal surgery on gastric emptying is

ameliorated by CGRP₈₋₃₇ or a monoclonal antibody to the peptide,^{140,141} which indicates that CGRP plays a transmitter role in the process of acute postoperative gastroparesis. Tachykinins may also play a role because a tachykinin receptor antagonist reduces short-term postoperative motor inhibition in the rat and hastens the return of myoelectrical activity.¹⁴⁴

Although short-term shutdown of gastrointestinal motility by surgery or chemical irritation can be viewed as protective response that prevents movements that could be deleterious to the traumatized gut, continued blockade of motor activity causes the clinical manifestations of ileus. The question as to which role peptidergic afferent neurons play in the prolonged, pathological form of postoperative and peritonitis-associated ileus has not yet been addressed.

Summary and Perspectives

Capsaicin-Sensitive Afferents as Neural Emergency System

Although capsaicin-sensitive afferent neurons participate in the physiological regulation of gastric functions, their primary role is to operate as a neural emergency system that is called into operation in the face of pending injury to the stomach but is not tonically active (Figure 6). As a result, blood flow to the stomach is greatly augmented, an effect that facilitates the delivery of bicarbonate to the surface epithelium and overlying mucus layer, adds to the removal of injurious factors from the mucosa, and promotes a wide range of processes that either reduce the vulnerability or aid the repair of the gastric mucosa.¹ In addition, stimulation of bicarbonate and mucus secretion and, under certain conditions, inhibition of acid output and motor activity also contribute to the overall protective role of capsaicin-sensitive afferents (Figure 6). This neural emergency system, which acts in concert with other mechanisms of protection,⁴³ is

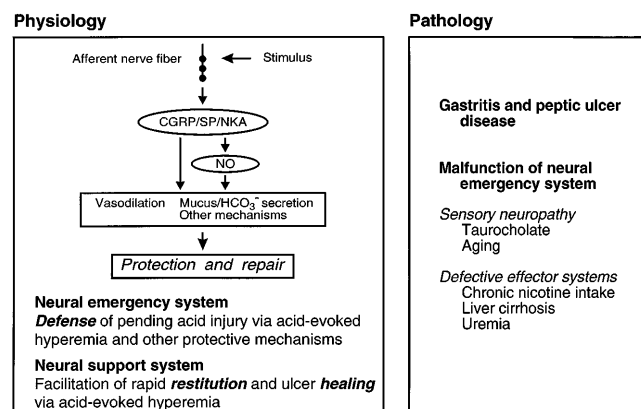


Figure 6. Schematic diagram of the physiological and pathophysiological implications of the neural emergency system in the stomach.

operative not only in the stomach but also in other regions of the gastrointestinal tract. Although most of the homeostatic actions are brought about by release of peptide transmitters from their peripheral endings, extrinsic sensory nerve fibers also constitute the afferent arc of autonomic reflexes that regulate secretory and motor functions.

Among the messenger molecules of afferent neurons, CGRP acting via CGRP₁ receptors and tachykinins acting via NK₂ receptors have proved to play a central role in enhancing mucosal resistance to pending injury. Both CGRP and tachykinins use NO as a secondary messenger. Furthermore, CGRP and NO are potent vasodilators that support protective mechanisms that depend on mucosal hyperemia by increasing GMBF. NKA, to the contrary, strengthens mucosal resistance to injury by promoting hyperemia-independent protective mechanisms. In addition, CGRP and other afferent neuron-derived peptides participate in the postoperative inhibition of gastric motility^{140,141,144} and in the pathophysiological regulation of gastric motor activity, secretion, and immunity.⁷⁰

In the long term, afferent neurons not only protect from pending injury but also facilitate repair processes, thus representing a neural support system for the rapid restitution of gastric erosions and the healing of ulcers (Figure 6). This function is envisaged from the delayed restitution and healing of gastric damage in rats pretreated with a neurotoxic dose of capsaicin.^{95,106,123,133}

Prejunctional and Postjunctional Defects of the Neural Emergency System

To put the functional characteristics of capsaicin-sensitive afferents into proper pathophysiological perspective, the conditions under which these neurons are stimulated and the functional consequences that may arise from a dysfunction of these neurons need to be considered. A variety of irritant chemicals including hydrochloric acid^{24,57,60,81} are able to excite capsaicin-sensitive afferent neurons either directly or indirectly via injury-induced formation or liberation of autacoids such as histamine, 5-hydroxytryptamine, prostanoids, leukotrienes, bradykinin, interleukin 1 β , platelet-activating factor, and endothelin 1.^{3,93,94,130,138,143,145} This wide spectrum of sensitivity to irritant and injurious factors puts capsaicin-sensitive afferent nerve fibers into a position that enables them to detect potentially harmful changes in their environment and to initiate appropriate measures of defense and repair.

The gastroprotective role of afferent neurons implies that improper functioning of this neural emergency

system is liable to weaken the resistance of the tissue to injury and may thus be an etiologic factor in gastroduodenal inflammation and ulcer disease. Evidence in favor of this conjecture is indeed accumulating, given that a prejunctional dysfunction of afferent nerve fibers (sensory neuropathy) or a postjunctional defect in the effector mechanisms disturbs gastric mucosal homeostasis (Figure 6). However, it needs to be emphasized that sensory neuropathies resulting from excessive intake of capsaicin-containing peppers are not known. To the contrary, it rather seems as if dietary chili intake is a factor that protects from peptic ulcer disease.¹¹²

A sensory neuropathy that weakens the neural emergency system in the stomach can be induced experimentally by bile salts (Figure 6) because long-term treatment of rats with oral taurocholate leads to a reduction of the capsaicin-evoked CGRP release and of the capsaicin-induced hyperemia in the gastric mucosa.¹⁴⁶ Furthermore, the capsaicin- and acid-evoked hyperemia in the rat gastric mucosa decreases with age, a change that is associated with a significant reduction in the density of CGRP-containing nerve fibers around arterioles in the gastric submucosa.¹⁴⁷ Hence, it is likely that a sensory neuropathy is in part responsible for the compromised ability of the aged gastric mucosa to defend itself against injurious factors.

Other disturbances of mucosal homeostasis are related to defects in the gastric effector systems that are under the control of afferent neurons (Figure 6). For instance, long-term administration of nicotine to rats suppresses the gastric hyperemic response to acid backdiffusion, a change that is associated with enhanced formation of vasoconstrictor leukotrienes in the rat stomach and, hence, may reflect a postjunctional depression of the acid-induced vasodilation.¹⁴⁸ The gastropathy caused by experimental cirrhosis¹⁴⁹ and uremia¹⁵⁰ is characterized by an inadequate increase of GMBF in response to capsaicin or acid backdiffusion through a leaky gastric mucosal barrier. Because the supply of gastric submucosal arterioles by CGRP-containing nerve fibers is unchanged in experimental cirrhosis¹⁴⁹ and uremia,¹⁵⁰ it can be inferred that the gastric circulatory dysregulation arises from a postjunctional defect.¹⁴⁹

From a pharmacological perspective, it needs to be borne in mind that drugs and medicines that influence the release, action, and metabolism of CGRP, NKA, and NO will interfere with the homeostatic function of peptidergic afferent neurons in the stomach. This is particularly true for CGRP and NKA receptor antagonists and NO synthase inhibitors. At the prejunctional

level, it is morphine and other opioid receptor agonists that inhibit the release of peptide transmitters from afferent nerve fibers and, in this way, enhance the vulnerability of the gastric mucosa to injury.^{5,57,93,102,122} The release of peptide transmitters from afferent nerve fibers may also be under the control of prejunctional adrenoceptors,⁵ but this possibility has not been explored yet in the stomach.

In summary, research fostered by the neuropharmacological potential of capsaicin has led to the discovery of a neural emergency system that is an important factor in the maintenance of gastric mucosal integrity. The work ahead must address the dynamics of peptidergic afferent neuron, their transmitters, receptors, and effectors in gastric diseases ranging from chronic gastritis, nonulcer dyspepsia, and peptic ulcer disease to the sensory disturbances and pain associated with functional disorders of the stomach.

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Address requests for reprints to: Peter Holzer, Ph.D., Department of Experimental and Clinical Pharmacology, University of Graz, Universitätsplatz 4, A-8010 Graz, Austria. Fax: (43) 316-380-9645.

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