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Neuropeptides, Inflammation, and Motility

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Neurogenic inflammation is a reaction which includes vasodilation, plasma extravasation, and smooth muscle contraction elicited by activation of and release of mediators from unmyelinated afferent nerve endings. Further release of inflammatory mediators follows activation of axon collaterals associated with these afferent nerve endings as axon reflexes. Substance P, somatostatin, vasoactive intestinal polypeptide, and calcitonin gene-related peptide are candidate mediators. Recent evidence suggests that several of these peptides may be colocalized either with one or more other peptides or with acetylcholine or noradrenalin. Communicating pathways exist between nerves within the mucosa and the muscle layers. Both long and short visceral reflexes occur. Inflammatory, mechanical, or chemical stimuli reaching the mucosa may release peptides from peripheral nerve endings. Thus neurogenic inflammation may be an important factor in inflammatory bowel disease.

KEY WORDS: substance P; primary afferent nerves; capsaicin.

A growing number of neuropeptides are being described in the enteric nervous system, the extrinsic innervation of the gastrointestinal tract, and regions of the central nervous system that regulate autonomic function (1–6). The concept of neuropeptides as mediators of "neurogenic inflammation" has been discussed in the context of polyarthritis and of inflammation of the eye, skin, and the respiratory tract (7–12), whereas the implication of neuropeptides in inflammatory changes in the gastrointestinal tract has received little attention (11, 13). The term neurogenic inflammation describes the reaction that includes vasodilatation, plasma extravasation, and smooth muscle contraction elicited by activation of and release of mediators from unmyelinated afferent (sensory) nerve endings (9, 14, 15). Antidromic activation of axon collaterals associated with these afferent nerve endings results in further release of inflammatory mediators. These "axon reflexes" may also produce changes in blood flow and smooth muscle contraction within the viscera (13, 16, 17). As will be discussed below, considerable evidence suggests that several neuropeptides, including substance P, somatostatin, vasoactive intestinal polypeptide, and calcitonin gene-related peptide may play a role in mediating this response. The following review will discuss current evidence supporting the hypothesis that neuropeptides play a role in the coregulation of motility and inflammatory mucosal lesions of the gastrointestinal tract.

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INTESTINAL MOTILITY AND MUCOSAL INFLAMMATION—CLINICAL EXAMPLES

Altered motility patterns of the stomach, small intestine, and colon have been described in associ-

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TABLE 1. INFLAMMATION AND GASTROINTESTINAL DYSMOTILITY

Hypermotility
Infectious diarrhea (ref 20, 26)
Gastric stress ulcerations (ref 19, 22)
Hypomotility
Intestinal pseudoobstruction (ref 25, 27)
Reflux esophagitis (ref 23, 31)
Ulcerative colitis (ref 18, 21, 24, 28–30)

ation with inflammatory and ulcerating conditions of the overlying mucosa (18–29). Depending on the pathologic condition, both hyper- and hypomotile patterns have been reported (Table 1).

One of the most common, yet little understood, examples is the development of localized or generalized ileus in association with inflammatory intraabdominal lesions such as pancreatitis, cholecystitis, or postoperatively. In ulcerative colitis, several investigators have described a colonic motility pattern of decreased phasic contractions associated with occasional high-amplitude contractions of prolonged duration (18, 24, 26, 29, 30). These latter contractions resulted in rapid propulsion of colonic contents, so-called mass movements. The response of the sigmoid colon to eating (gastrocolonic response) was significantly altered in patients with ulcerative colitis (28). Even though the electrical control activity of the sigmoid colon was intact, the mechanical response was almost abolished. In contrast, others described a hypermotile pattern and increased tonus changes of the distal colon from patients with ulcerative colitis in response to opioids (21). In toxic megacolon, a complete loss of phasic and tonic activity of colonic muscle is observed.

Several authors have reported intestinal dysmotility patterns both in man and in animal models with inflammatory lesions of the small bowel. Mucosal inflammatory changes have been reported in patients with chronic intestinal pseudoobstruction, and both mucosal changes and altered motility patterns have been described in the excluded small bowel of patients after jejunoileal bypass surgery (25, 27). Enteric parasites, enteropathogenic bacteria, and bacterial toxins have all been implicated as causing abnormal patterns of gastrointestinal motility (20, 26).

In the stomach, different authors have implicated altered gastric motility patterns in the pathogenesis of stress ulcerations (22). Decreased mucosal blood flow due to high-amplitude contractions was suggested as a possible mechanism.

In the esophagus, decreased peristalsis and a decrease in the lower esophageal sphincter pressure associated with reflux esophagitis have been reported in humans and animal models (23, 31). A role of prostaglandins as mediators of the dysmotility has been suggested.

In the great majority of these examples of dysmotility patterns associated with inflammatory or ulcerating gastrointestinal lesions, it remains to be defined if the observed dysmotility is the primary or secondary event, and which mechanisms and pathways are involved. The hypermotility pattern seen in certain forms of infectious diarrhea suggests a teleological role in producing a more rapid clearance of infectious agents and/or their toxic products from the intestine. Since such a mechanism would provide a significant evolutionary survival advantage, mechanisms and pathways providing a communication between nociceptive mucosal stimuli and propulsive intestinal contractions are likely to be present in the gastrointestinal tract. In the following, we will focus on the anatomical and functional evidence that inflammatory changes within the mucosa may affect motility or that both inflammatory and motility changes may be produced by similar mechanisms.

PEPTIDERGIC PATHWAYS BETWEEN MUCOSA AND MUSCLE—MORPHOLOGICAL EVIDENCE

Numerous neuropeptides have been identified in the mucosa and muscle layer of the gastrointestinal tract of different mammals, including man (5). Throughout the intestinal mucosa, vasoactive intestinal polypeptide-containing fibers are the most numerous, with lesser numbers containing substance P, somatostatin, neuropeptide Y, and enkephalin. More recent evidence suggests that several of these peptides may be colocalized either with one or more of the other peptides or with acetylcholine or noradrenaline (2). The majority of corresponding nerve cell bodies is located in the submucous plexus.

Communicating pathways between nerves within the mucosa and the muscle layers occur in the form of direct projections of neurons from one layer to another layer or in the form of reflex pathways with synapses within the bowel wall, in the spinal cord, or in the brain stem. A population of neurons innervating the mucosa have their cell bodies in the myenteric plexus (2). In the canine colon, certain submucous ganglion cells have direct projections to

the muscle layer, providing a cholinergic input to the circular muscle layer, modulating its slow-wave activity (32).

Certain efferent and afferent nerve fibers innervating the gastrointestinal tract have their cell bodies outside the bowel wall. The cell bodies for these primary sensory afferents are located either in the dorsal root ganglia (for spinal afferents) or in the nodose ganglia (for vagal afferents), whereas the cell bodies for extrinsic efferent nerves lie in sympathetic ganglia and in the dorsal vagal motor nucleus in the brain stem. In the gastrointestinal tract, primary sensory nerves form the perivascular nerve plexus, some large varicose nerve fibers in the submucous ganglia, and probably some nerve fibers within the myenteric plexus (2, 13, 33–35). The pattern of vascular innervation shows marked regional differences with a particularly dense innervation around arterioles and capillaries and sparing of veins (34). Even though substance P accounts for most of the immunoreactivity in the peripheral branches of the primary sensory neuron, somatostatin and calcitonin gene-related peptide are also present. Primary sensory neurons can provide communications between different parts and elements of the gastrointestinal tract in several ways.

VISCEROVISCERAL REFLEXES—FUNCTIONAL EVIDENCE

Viscerovisceral reflex pathways participate in reflex changes in motility, secretion, and blood flow in response to physiological stimuli. There are long and short reflex arcs with afferent pathways located in the spinal nerves and in the vagus. Long reflexes have synapses within the central nervous system and mediate reflex changes in response to such noxious stimuli as excessive pressure on the mesentery or intraperitoneal injection of bradykinin (2, 16, 31). Short reflex arcs involve axon collaterals that make synaptic contact with post ganglionic inhibitory sympathetic nerves (13, 16, 37). One reflex thought to be mediated in this way is the decrease in gastric motility in response to acid in the jejunum (13).

Functional and morphological evidence has shown that the gastrointestinal tract is innervated by spinal and vagal capsaicin-sensitive afferent fibers (13, 14, 16, 19, 33, 35, 38–41). Capsaicin is a neurotoxin that is highly specific for nonmyelinated afferent nerve fibers (38). Thus, the inhibition of gastric and intestinal motility in rats in response to surgical trauma and intraperitoneal injection of bradykinin was significantly reduced following neonatal capsaicin treatment, suggesting the involvement of primary sensory nerves (16, 42). Capsaicin-sensitive afferents have been implicated in gastric mucosal protection against ulcerogenic factors, such as indomethacin, cysteamine, and acid (17, 43).

Antidromic stimulation of afferent nerve fibers can have excitatory effects on intestinal motility. Stimulation of sensory nerves by capsaicin (applied either from the mucosal or serosal side) or heating has been shown to contract gastric, ileal, and colonic smooth muscle by release of substance P, which in turn stimulates cholinergic myenteric nerves (13, 36). In the rat duodenum, capsaicin produces afferent stimulation via release of calcitonin gene-related peptide (33, 44).

In summary, sensory afferent nerves participate in the regulation of gastrointestinal motility in response to mucosal irritation via short and long viscerovisceral reflexes and possibly via intramural axon reflexes. Experimental evidence suggests that the resulting motility response can be either inhibitory or excitatory.

NEUROGENIC INFLAMMATION—EVIDENCE FROM TISSUES OTHER THAN THE GASTROINTESTINAL TRACT

It has been suggested that peptidergic, primary sensory nerves around blood vessels fulfill several different functions. Besides being carriers of sensory information and local regulators of tissue perfusion, they appear to mediate the process of neurogenic inflammation (8, 19, 34, 35). It has been known for a long time that sensory neurons of the skin are involved in local reactions to noxious stimuli of a mechanical, physical, or chemical nature (7, 9, 15). These local reactions consist of hyperemia, plasma extravasation, and smooth muscle contraction, and they appear to be mediated by sensory nerves via axoaxonic reflexes. The putative role of substance P as the mediator of this neurogenic inflammation induced by various nociceptive stimuli has been postulated from studies in many different tissues including the dental pulp, skin, eye, joints, respiratory tract and certain parts of the gastrointestinal tract (9). The assumption that substance P is one of the primary mediators of neurogenic inflammation is based on the following observations (15): Substance P is associ-

TABLE 2. INTERACTION BETWEEN SUBSTANCE P AND OTHER MEDIATORS OF NEUROGENIC INFLAMMATION*

Organ	*Mediator*	*Modulation of SP effect*
Bronchial tree	Prostaglandins	Inhibit airway edema and bronchoconstriction
Eye	Prostaglandins Histamine	Induce release of SP from sensory nerves
Skin	Histamine	Released by SP from mast cells
Nasal mucosa	VIP Acetylcholine	Cause neurogenic inflammation
Hind paw	Somatostatin [D-Met^2, Pro^5] enkephalinamide	Inhibit neurogenic inflammation
Skin	CGRP	Potentiate SP effect

*Modified from F Lembeck, 1982 (ref 9).

ated with those sensory nerve fibers which are involved in antidromic vasodilation. Substance P is released from the peripheral terminals of these sensory neurons during antidromic stimulation. Local mechanical, chemical, and physical irritants cause a release of substance P, resulting in neurogenic inflammation. Arterial administration or topical application of substance P causes vasodilation, plasma extravasation, and smooth muscle contraction. Capsaicin depletes substance P from chemosensitive primary afferents and blocks antidromic vasodilation, plasma extravasation, and smooth muscle contraction.

Despite this convincing evidence for a role of

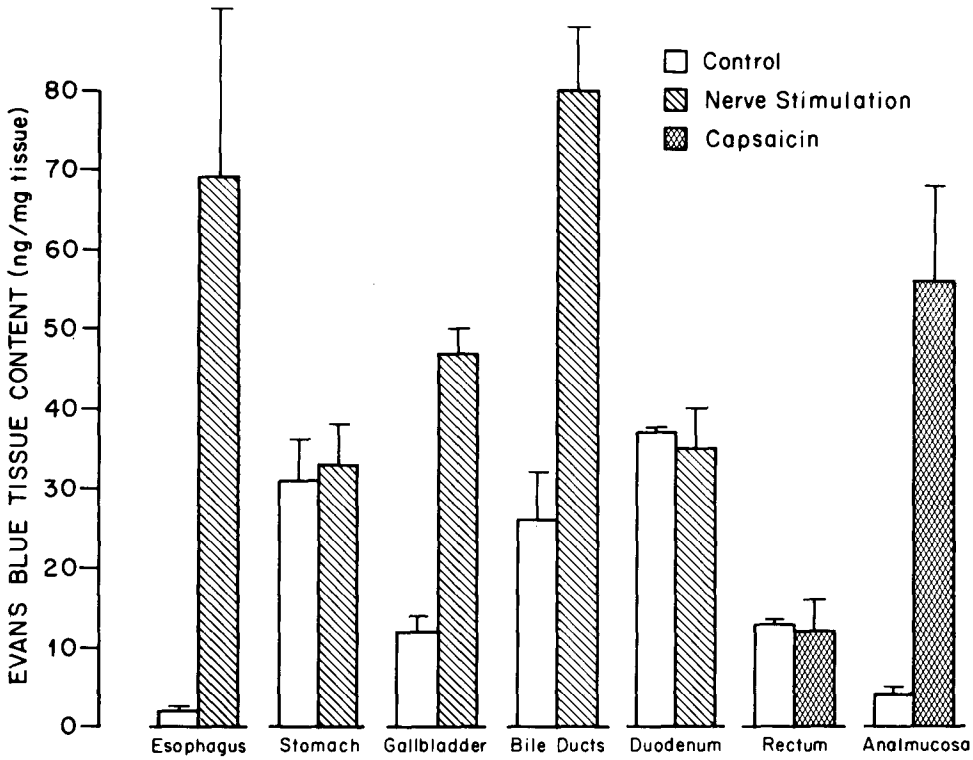

Fig 1. Plasma extravasation in the guinea pig gastrointestinal tract in response to antidromic nerve stimulation or intravenous capsaicin. Plasma extravasation was quantified by measuring Evans blue tissue content with or without excitation of sensory afferents. Tissue extravasation was only observed in the esophagus and in the anal mucosa, not in the stomach, duodenum, or rectum. Modified from Lundberg et al, 1984 (ref 40).

substance P, other compounds appear to be involved in the pathogenesis of neurogenic inflammation (9, 46, 47) (Table 2). Prostaglandins have been described as coregulators of the neurogenic inflammatory response at least in two other tissues: the bronchial system and the eye. Substance P afferents are involved in airway edema and bronchoconstriction induced by vagal stimulation and local irritation (15). In bronchial smooth muscle, indomethacin potentiates the contractile response to substance P, suggesting an antagonistic action of prostaglandins on neurogenic inflammation. No interaction could be demonstrated between substance P and leukotrienes in the bronchial system. In the rabbit eye, both prostaglandins and histamine were found to release substance P from sensory nerve terminals (14), whereas in the skin, neurogenic inflammation appears to be partially mediated by substance P-induced histamine release from mast cells (8). In the nasal mucosa, neurogenic vasodilation is mediated not only by substance P but also by the release of acetylcholine and VIP (15). The release of substance P from sensory nerve endings is inhibited by opioids and noradrenaline and enhanced by naloxone (13). Somatostatin and [D-Met^2,Pro^5]-enkephalinamide were found to inhibit neurogenic vasodilation and plasma extravasation induced by saphenous nerve stimulation in the rat (48), whereas calcitonin gene-related peptide was found to potentiate plasma protein extravasation induced by mammalian tachykinins in the rat abdominal skin (49). The latter finding is of particular interest since calcitonin gene-related peptide appears to be colocalized with substance P in primary sensory afferents (2).

NEUROGENIC INFLAMMATION—EVIDENCE FROM THE GASTROINTESTINAL TRACT

In contrast to other tissues, little is known about the role and mechanisms of neurogenic inflammation within the gastrointestinal tract. Noxious stimulation of the gastric mucosa by warming to 45–52 ° C was found to stimulate gastric contractions (19). This stimulation was said to activate axon reflexes by which substance P is released from sensory collaterals in the vicinity of myenteric nerve cell bodies. However, in the gastrointestinal tract of the guinea pig, the neurogenic inflammatory response to antidromic stimulation of the splanchnic and pelvic nerves or the mesenteric ganglion and to systemic substance P or capsaicin was limited to the esophagus, the anal canal, the gallbladder, and bile ducts (Figure 1). No effect was seen in the stomach, duodenum, and large and small intestine with sharp demarcation zones between affected and unaffected areas (40). It remains unclear if these findings are species specific, are due to lack of cofactors, or indicate that neurogenic inflammation does not occur in the majority of the gastrointestinal tract.

In summary, primary sensory neurons play a dual role in the local defense mechanisms to injury. Whereas the central terminals transmit pain sensation to the central nervous system, the peripheral terminals may mediate a local inflammatory response via the axon reflex. Depending on the tissue involved and the type of injury, several neuropeptides and other compounds seem to mediate this response.

SUMMARY

Considerable clinical and experimental evidence suggests the presence of regulatory mechanisms

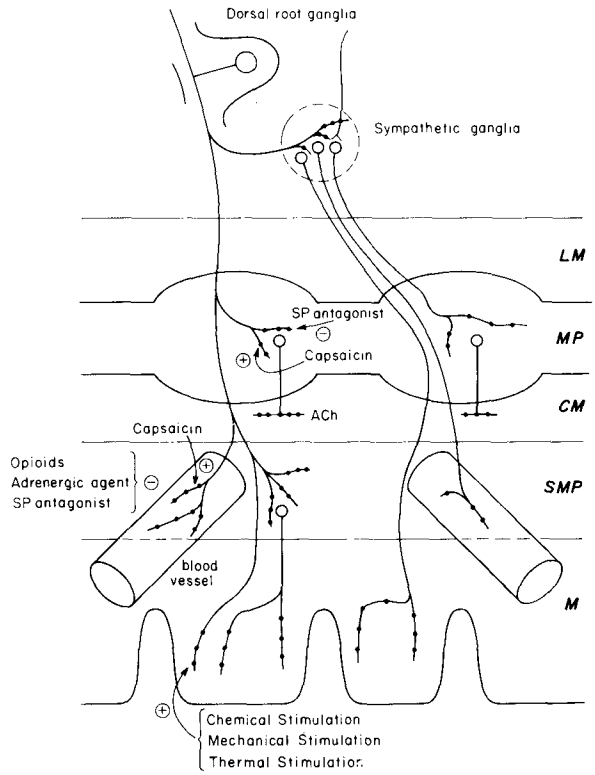

Fig 2. Schematic diagram showing reflex pathways between afferent nerves (left) and efferent sympathetic nerves in the guinea pig small intestine. LM, longitudinal muscle; MP, myenteric plexus; CM, circular muscle, SMP, submucous plexus; M, Mucosa. Modified from Costa et al, 1987 (ref 2)

linking noxious mucosal events with changes in the contractile response of the gastrointestinal tract. Sensory peptidergic neurons could form an important component of the circuitry mediating this nociceptive response (Figure 2). Besides being part of a variety of intramural, peripheral, and central reflexes, primary afferent nerves may provide the circuitry integrating several different gastrointestinal responses. Inflammatory, mechanical, or chemical stimuli reaching the intestinal mucosa may cause a release of substance P and other peptides from these peripheral nerve endings, thereby altering motility of the muscularis mucosae, local blood flow, and possibly gastrointestinal secretion and absorption. Further changes in the function of gastrointestinal muscle and mucosa could occur as a result of altered blood flow. A better understanding of the role and physiology of the sensory branch of the enteric nervous system could provide important insights into motility abnormalities and pain syndromes associated with inflammatory conditions of the gastrointestinal tract.

REFERENCES

1. Costa M, Furness JB: Nervous control of intestinal motility. *In* Handbook of Experimental Pharmacology. G Bertaccini (ed). Berlin, Springer, 1982, Chap 10
2. Costa M, Furness JB, Llewellyn-Smith IJ: Histochemistry of the enteric nervous system. *In* Physiology of the Gastrointestinal Tract, LR Johnson (ed). New York, Raven, 1987, Chap 1
3. Dockray GJ: Physiology of enteric neuropeptides. *In* Physiology of the Gastrointestinal Tract. LR Johnson (ed). New York, Raven, 1987, Chap 2
4. Furness JB, Costa M: Identification of gastrointestinal neurotransmitters. *In* Handbook of Experimental Pharmacology, Vol 59/1. G Bertaccini (ed). Berlin, Springer, 1982, Chap 11
5. Keast JR, Furness JB, Costa M: Distribution of certain peptide-containing nerve fibers and endocrine cells in the gastrointestinal mucosa in five mammalian species. J Comp Neurol 236:403–422, 1985
6. Morrison JFB: (1977) The afferent innervation of the gastrointestinal tract. *In* Nerves and the Gut. FP Brooks and PW Evers (eds). New Jersey, Charles B. Slack, 1977, pp 297–322
7. Hagermark O, Hokfelt T, Pernow B: Flare and itch induced by substance P in human skin. J Invest Dermatol 71:233–235, 1978
8. Lembeck F, Holzer P: Substance P as neurogenic mediator of antidromic vasodilation and neurogenic plasma extravasation. Naunyn-Schmiedeberg's Arch Pharmacol 310:175–183, 1979
9. Lembeck F: Substance P and sensory neurones. *In* Substance P. Metabolism and Biological Actions. CC Jordan, P Oehme (eds). London, Taylor and Francis, 1985, pp 137–151
10. Levine JD, Moskowitz MA, Basbaum AI: The contribution of neurogenic inflammation in experimental arthritis. J Immunol 135:843s–846s, 1985
11. Lotz M, Carson DA, Vaughan JH: Substance P activation of rheumatoid synoviocytes: Neural pathway in pathogenesis of arthritis. Science 235:893–895, 1987
12. Mandahl A, Bill A: Ocular responses to antidromic trigeminal stimulation, intracameral prostaglandin E_1 and E_2, capsaicin and substance P. Acta Physiol Scand 112:331–338, 1981
13. Bartho L, Holzer P: Search for a physiological role of substance P in gastrointestinal motility. Neuroscience 16:1–32, 1985
14. Pernow B: Substand P. Pharmacol Rev 35:85–141, 1983
15. Pernow B: Sutstance P: Present status and future prospects. *In* Substance P. Metabolism and Biological Actions. CC Jordan, P Oehme (eds). London, Taylor and Francis, 1985, pp 187–196
16. Cervero F, McRitchie HA: Neonatal capsaicin does not affect unmyelinated efferent fibers of the autonomic nervous system: Functional evidence. Brain Res 239:283–288, 1982
17. Holzer P, Sametz W: Gastric mucosal protection against ulcerogenic factors in the rat mediated by capsaicin-sensitive afferent neurons. Gastroenterology 91:975–981, 1986
18. Chaudhary NA, Truelove SC: Human colonic motility: A comparative study of normal subjects, patients with ulcerative colitis and the irritable bowel syndrome. Gastroenterology 40:11–17, 1961
19. Delbro D, Lisander B, Anderson SA: Atropine-sensitive gastric smooth muscle excitation by mucosal nociceptive stimulation—the involvement of an action reflex? Acta Physiol Scan 122:621–627, 1984
20. Fox-Robichaud AE, Collins SM: Altered calcium-handling properties of jejunal smooth muscle from the nematode-infested rat. Gastroenterology 91:1462–1469, 1986
21. Garret JM, Sauer WG, Moertel CG: Colonic motility in ulcerative colitis after opiate administration. Gastroenterology 53:93–100, 1967
22. Garrick T, Leung FW, Buack S, Hirabayashi K, Guth PH: Gastric motility is stimulated but overall blood flow is unaffected during cold restraint in the rat. Gastroenterology 91:141–148, 1986
23. Higgs RH, Castell DO, Eastwood GL: Studies on the mechanism of esophagitis-induced lower esophageal sphincter hypotension in cats. Gastroenterology 71:51–56, 1976
24. Kern F Jr, Almy TP, Abbot FK, Boggdonoff MD: The motility of the distal colon in nonspecific ulcerative colitis. Gastroenterology 19:492–503, 1951
25. Mayer EA, Schuffler MD, Rotter JI, Hanna P, Mogard M: Familial visceral neuropathy with autosomal dominant transmission. Gastroenterology 91:1528–1535, 1986
26. Read NW: Diarrhee motrice. *In* Clinics in Gastroenterology, Vol 15/3. GJ Krejs (ed). Philadelphia, Saunders, 1986, Chap 10
27. Schuffler MD, Kaplan LR, Johnson L: Small intestinal mucosa in pseudo-obstruction syndromes. Am J Dig Dis 23:821–828, 1978
28. Snape WJ Jr, Matarazzo SA, Cohen S: Abnormal gastrocolonic response in patients with ulcerative colitis. Gut 21:392–396 1980
29. Spriggs EA, Code CF, Bargen JA, Curtiss RK, Hightower NC Jr: Motility of the pelvic colon and rectum of normal

persons and patients with ulcerative colitis. Gastroenterology 19:480–491, 1951
30. Almy TP: Observations on the pathologic physiology of ulcerative colitis. Gastroenterology 40:299–306, 1961
31. Kahrilas PJ, Dodds WJ, Hogan WJ, Kern M, Arndorfer RC, Reece A: Esophageal peristaltic dysfunction in peptic esophagitis. Gastroenterology 91:897–904, 1986
32. Sanders KM, Smith TK: Mononeurones of the submucous plexus regulate electrical activity of the circular muscle of canine proximmal colon. J Physiol 380:293–310, 1986
33. Costa M, Furness JB, Llewellyn-Smith IJ, Murphy R, Bornstein JC, Keast JR: Functional roles for substance P-containing neurones in the gastrointestinal tract. *In* Substance P. Metabolism and Biological Actions. CC Jordan, P Oehme (eds). London, Taylor and Francis, 1985, pp 99–119
34. Feher E, Burnstock G: Ultrastructural localization of substance P, vasoactive intestinal polypeptide, somatostatin and neuropeptide Y immunoreactivity in perivascular nerve plexuses of the gut. Blood vessels 23:125–136, 1986
35. Furness JB, Papka RE, Della NG, Costa M, Eskay RL: Substance P-like immunoreactivity in nerves associated with the vascular system of guinea-pigs. Neuroscience 7:447–459, 1982
36. Bartho L, Holzer P, Lembeck F, Szolcsanyi J: Evidence that the contractile response of the guinea-pig ileum to capsaicin is due to substance P. J Physiol 332:157–167, 1982
37. Wood JD: Physiology of the enteric neurons system. *In* Physiology of the Gastrointestinal Tract. LR Johnson (ed). New York, Raven, 1987, Chap 3
38. Buck SH, Burks TF: The neuropharmacology of capsaicin: Review of some recent observations. Pharmacol Rev 38:179–226, 1986
39. Lembeck F, Skotfish G: Visceral pain reflex after pretreatment with capsaicin and morphine. Naunyn-Schmiedebergs Arch Pharmacol 321:116–122, 1982
40. Lundberg JM, Brodin E, Hua X, Saria A: Vascular permeability changes and smooth muscle contraction in relation to capsaicin-sensitive substance P afferents in the guinea pig. Acta Physiol Scand 120:217–227, 1984
41. Bartho L, Szolcsanyi J: Local chemoreflexes of the guinea Pig ileum elicitied by sensory stimulating agents. Acta Physiol Hung 52:200, 1978
42. Holzer P, Lippe IT, Holzer-Petsche V: Inhibition of gastrointestinal transit due to surgical trauma on peritoneal irritation is reduced in capsavesh-treated rate. Gastroenterology 91:360–336, 1986
43. Szolcsanyi J, Bartho L: Impaired defense mechanism to peptic ulcer in the capsaicin-desensitized rat. *In* Advances in Physiological Science, Vol 15, Gastrointestinal Defense Mechanisms. Mozsik, O Haenninen, T Javor (eds). New York, Pergamon Press, 1981, pp 39–51
44. Maggi CA, Manzini S, Giuliani S, Santicioli P, Meli A: Extrinsic origin of the capsaicin-sensitive innervation of rat duodenum: Possible involvement of calcitonin-gene-related peptide (CGRP) in the capsaicin-induced activation of intramural nonadrenergic noncholinergic neurons. Naunyn-Schmiedebergs Arch Pharmacol 334:172–180, 1986
45. Rozsa Z, A Varro, G Jansco: Use of immunoblockade to study the involvement of peptidergic afferent nerves in the intestinal vasodilating response to capsain in the day. Eur J Pharmacol 115:59–63, 1985
46. Gamse R, Lackner D, Gamse G, Leeman SE: Effect of capsaicin pretreatment on capsaicin-evoked release of immunoreactive somatostatin and substance P from primary sensory neurons. Naunyn-Schmiedebergs Arch Pharmacol 316:38–41, 1981
47. Lembeck F, Donnerer J: Opioid control of the function of primary afferent substance P fibres. Eur J Pharmacol 114:241–246, 1985
48. Lembeck F, Donnerer J, Bartho L: Inhibition of neurogenic vasodilatation and plasma extravasation by substance P antagonists, somatostatin and [D-MET2,PRO5]enkephalinamide. Eur J Pharmacol 85:171–176, 1982
49. Gamse R, Saria A: Potentiation of tachykinin-induced plasma protein extravasation by calcitonin gene-related peptide. Eur J Pharmacol 114:61–66, 1985