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REVIEW

Role of Afferent Sensory Neurones in Gastric Injury/Protection

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Summary

The role of afferent sensory neurones in gastric mucosal protection is discussed. The principal effects of substance P and capsaicin on gastric motility and mucosal blood flow are taken in correlation with gastric mucosal injury. It seems likely that the protective effect of sensory neuropeptides is dependent on gastric mucosal blood flow and is mediated through the nitric oxide-generating system and partly the prostaglandins. The interaction between these two systems and the primordial effect of one of them on gastric mucosal blood flow and mucosal integrity after neuropeptide release is still not clear.

Key words

Substance P – Capsaicin – Prostaglandins – Gastric injury – Gastric blood flow – Nitric oxide – Motility

Introduction

Substance P (SP), an undecapeptide originally isolated from the intestine, is known as a neurotransmitter and neuromodulator in the central and peripheral nervous systems and belongs to the family of tachykinins. Besides its functions in mediating physiological signal transmission, e.g. the dilation of cerebral arteries (Edvinsson *et al.* 1981), contraction of the hepatic portal vein (Hellstrand and Järhult 1980) and stimulation of smooth muscle cells (Couture and Regoli 1982), this peptide seems to play an important role in several pathological processes, such as bronchial constriction and inflammation (Lundberg *et al.* 1983), or pain transmission (Lembeck *et al.* 1981). As mentioned above, the principal vascular activity of SP is dilatation which is evident in systemic arteries and arterioles (Pernow 1983) and the contraction of smooth muscle cells preferentially demonstrated in the gut (Pernow 1963).

In the present paper, we review the possible effects of these two principal properties of SP on gastric mucosal protection. Additionally, we discuss the dual effects of capsaicin on afferent sensory neurones in the gastric mucosa. The relationship of capsaicin and SP is stressed because of the pharmacological properties of capsaicin relating to the sensory neuropeptides.

Substance P-mediated signal transmission

The source of SP in mammalian tissues are sensory nerve fibres. The intraneuronal SP is transported towards the terminal regions of these peripheral nerve branches, where it is stored in nerve endings. The release of SP and other peptides from peptidergic nerve endings mediates vascular and smooth muscle activities (Pernow 1983).

The effect of divers tachykinins is transmitted through three major receptor subtypes, named NK-1 (SP-P), NK-2 (SP-E) and NK-3 (SP-N) (Maggi *et al.* 1990, Lee *et al.* 1982, 1986). The specific affinities of these receptors correspond to SP, neurokinin A and neurokinin B, respectively (Guard and Watson 1991).

The studies of the conformational orientation of several tachykinin C-terminal heptapeptides revealed that the tertiary structures of different tachykinins are highly variable. However, the

conformational structure of a part of the alpha-helix in SP (-Phe-Phe-Gly- Leu-) is common to all tachykinins and is believed to be an important sequence in SP-binding to NK-1 receptors (Payan 1989). This may also indicate that neurokinin A and B can stimulate NK-1 receptor activity at higher concentrations (Cotrait and Hospital 1986).

Substance P binding to its receptor increases phosphatidyl-inositol hydrolysis through phospholipase C activation. Inositol phospholipid metabolism, subsequent protein kinase C stimulation and the rise in intracellular Ca^{2+} seem to be the primary receptor-coupling mechanisms in signal transduction initiated by SP and other tachykinin binding (Payan 1985, Gimenez-Gallego *et al.* 1985).

Role of substance P in regulation of gastrointestinal motility and gastric mucosal blood flow

In the gastrointestinal tract, a dense network of SP-I fibres was found in the myenteric plexus and smooth muscle layers. For studying the involvement of these sensory neurones in organ function, capsaicin has been used as a potent pharmacological tool (Buck and Burks 1986, Holzer 1988). Immunohistochemical studies have shown that capsaicin-sensitive afferent neurones innervating the rat stomach contain SP (Green and Dockray 1987). SP-immunoreactive neurones in the stomach wall are concentrated in the greater curvature (Minagawa *et al.* 1984). These SP-I fibrers in the smooth muscle layers originate from the SP-I cells in the myenteric ganglia and run parallel to the circular and longitudinal muscle layers throughout the entire stomach (Minagawa *et al.* 1984). The excitatory effects of SP on smooth muscles (Pernow 1953, Bury and Mashford 1980, Rosell *et al.* 1977, Yau 1978, Holzer and Lembeck 1979, 1980, Sasaki 1979, Holzer *et al.* 1980, Bauer and Kuriyama 1982) concern physiological transmission (Franco *et al.* 1979, Costa *et al.* 1985, Bartho *et al.* 1982 a,b, 1989, Llewellyn-Smith *et al.* 1988, 1989, Holzer 1989) as well as spasmogenic action in the guinea-pig ileum (Maggi *et al.* 1990). The effect of SP on guinea-pig ileum was dose-dependent and evoked muscle contractions of both longitudinal and circular smooth muscle layers (Ohmori *et al.* 1993). Moreover, the release of SP was demonstrated in the venous effluent in response to peristaltic contractions (Donnerer *et al.* 1984). However, an antagonistic effect was found in the rat stomach, where intragastric administration of capsaicin significantly inhibited gastric motility (Takeuchi *et al.* 1991a).

The role of SP in the control of gastric mucosal blood flow is widely accepted today. The effect of capsaicin reflects its dual action and depends on the mode of pretreatment. Activation of sensory nerve fibres by acute intragastric administration of capsaicin increases gastric mucosal blood flow (Lippe *et al.* 1989b, Holzer *et al.* 1990b, 1991). On the other hand, the ablation of gastric afferent neurones by chronic capsaicin or morphine-mediated block of SP release was associated with inhibition or abolition of gastric mucosal blood flow (Holzer *et al.* 1991). It was concluded that capsaicin-sensitive sensory neurones in the gastrointestinal tract can cause vasodilation *via* an axon reflex (Rózsa and Jacobson 1989). It is consistent with the presence of vasodilator peptides such as SP and calcitonin-gene-related peptide (CGRP) in these neurones (Su *et al.* 1987, Sternini *et al.* 1987, Green and Dockray 1988, Bauerfeind *et al.* 1989).

Substance P and gastric mucosal injury

It was generally accepted that both smooth muscle contraction and gastric mucosal blood supply play an important role in the pathogenesis of gastric mucosal injury, and SP seems to be prominently involved in this pathological process. Several years ago it was reported that centrally administered SP had no demonstrable effect on the development of gastric mucosal lesions (Nakane *et al.* 1985). Similarly, in ethanol-induced gastric injury the subcutaneous application of SP did not inhibit production of lesions (Evangelista *et al.* 1987b). Moreover, increased levels of SP have been reported in the proximal duodenum of duodenal ulcer patients (Domschke *et al.* 1985).

Contrary to this, the protective effect of tachykinins, such as SP and CGRP, on gastric mucosa against ethanol injury has been reported (Holzer *et al.* 1989, 1990a, Holzer and Lippe 1988, Russel and Burchiel 1984, Evangelista *et al.* 1989, Maggi *et al.* 1987). However, the protective role of these peptides seems to be dependent on the experimental conditions and the mode of pretreatment. The inhibition of ethanol-induced gastric lesions was observed after acute oral administration of capsaicin, while capsaicin-sensitive afferent nerve degeneration attenuated this protective effect (Uchida *et al.* 1991b). This raised the question, how to explain the possible mechanisms involved in the tachykinin-mediated influence on gastric functions in view of this mucosal protection?

Few years ago, the importance of gastric motility in the pathogenesis of indomethacin-induced gastric injury was proposed (Takeuchi *et al.* 1986, 1989). Gastric motility was also suggested as a major factor in cold restraint-induced lesion formation in rats (Garrick *et al.* 1986). The gastric mucosal injury seems to depend on the amplitude and duration of gastric smooth muscle contraction. Since it is known that strong gastric contractions can effectively reduce or arrest gastric mucosal blood flow (Livingston *et al.* 1991) and that adequate blood flow is essential for the maintenance of mucosal integrity (Leung *et al.* 1985), this suggests that there exists a direct link between gastric motility and gastric mucosal blood flow in mediating stomach protection.

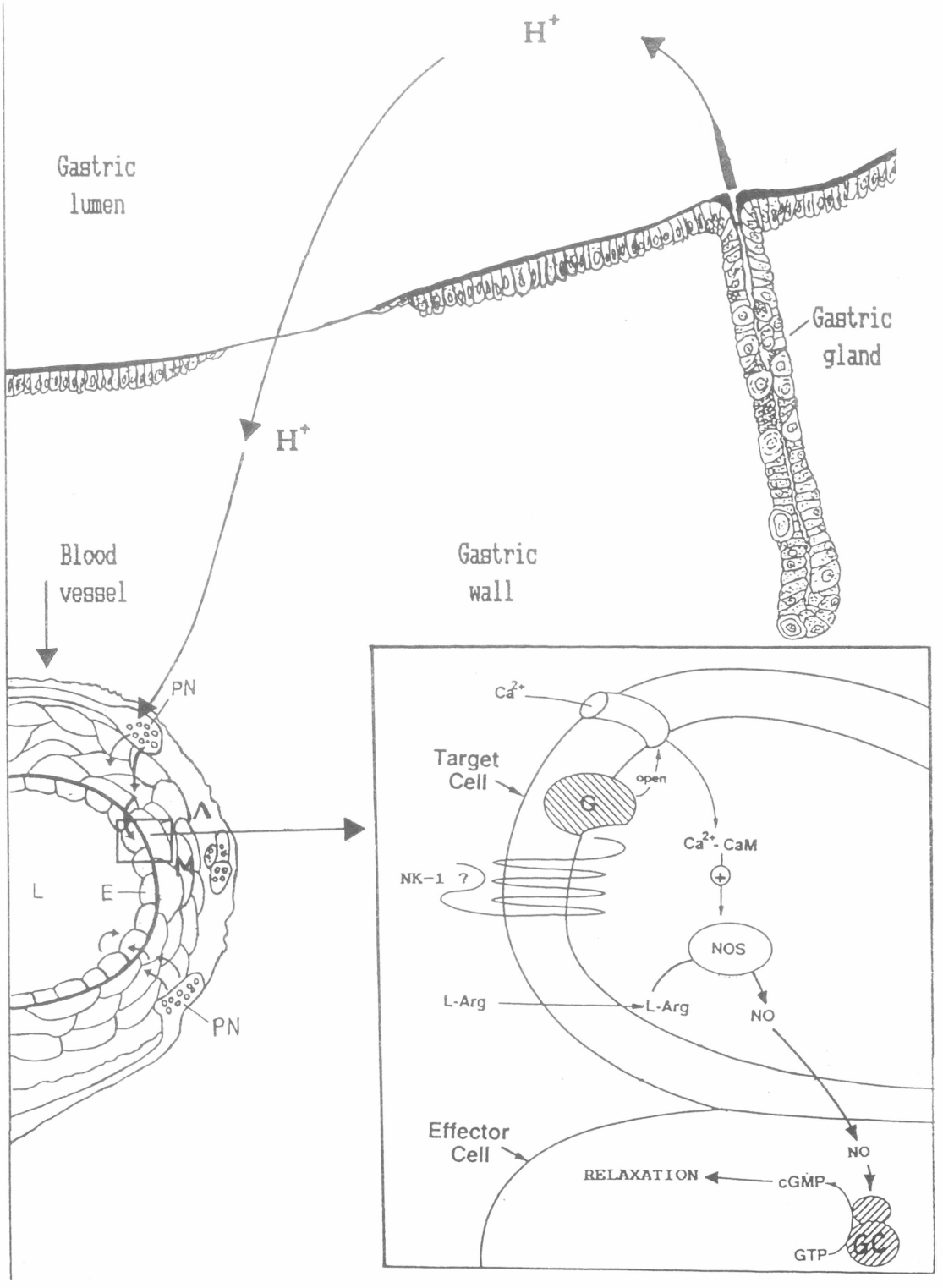

Fig. 1
Transcellular signalling after gastric mucosal barrier disruption. Activation of afferent sensory peptidergic neurones (PN) by retrodiffusion of H^+ results in neuropeptide release from nerve endings. Subsequent stimulation of peptidergic receptors (NK-1) in endothelial target cells (E) augments cytosolic Ca^{2+} levels and through calmodulin (CaM) increases NO-synthase (NOS) activity. The release of nitric oxide (NO), derived from the oxidative metabolism of L-arginine (L-Arg) induces activation of the soluble form of guanylate cyclase (GC) and mobilization of the cGMP cascade in adjacent smooth muscle effector cells (M). The final effect is relaxation and blood vessel dilatation.

The transient but significant enhancement in gastric motility was also observed during 15 min period after capsaicin administration (Holzer *et al.* 1991), but a controversial, gastric motility inhibiting effect was also observed (Takeuchi *et al.* 1991a). Because the mucosal blood flow at the same time increases after capsaicin, it seems likely that the influence of SP and other tachykinins on stomach contractility is not the main mechanism in preventing gastric mucosal injury. A more probable effect of capsaicin-sensitive sensory neurones in the pathogenesis of gastric mucosal damage concerns the control of gastric mucosal blood flow. The stimulation of peripheral endings of capsaicin-sensitive nerves which release the vasodilatory peptides such as SP and CGRP (Renzi *et al.* 1991, Holzer *et al.* 1990a), as well as acute administration of these peptides, prevented ethanol- or indomethacin-induced gastric mucosal damage (Evangelista *et al.* 1989, Maggi *et al.* 1987, Lippe *et al.* 1989a). This protection was directly related to significantly increased gastric mucosal blood flow (Holzer and Lippe 1988, Holzer *et al.* 1989). Thus, the increase of gastric mucosal blood flow has been proposed as a mechanism of the gastroprotection induced by capsaicin (Holzer *et al.* 1991, Lippe *et al.* 1989b). Moreover, this idea is supported by the finding that capsaicin-sensitive nerve degeneration weakens gastroprotection presumably by the decrease of gastric mucosal blood flow through the decrease of SP- and CGRP-immunoreactive substances (Holzer and Sametz 1986, Evangelista *et al.* 1987a, Uchida *et al.* 1993). However, differences have been observed in the corpus and antrum (Uchida *et al.* 1991a).

Further evidence suggests that capsaicin-sensitive sensory neurones regulate the mechanisms of gastric mucosal protection by monitoring H^+ ion reflux diffusion into the gastric mucosa and in turn signalling submucosal arterioles to facilitate gastric mucosal blood flow (Fig. 1). Based on this background, it was suggested that sensory neurones constitute an essential link between gastric mucosal barrier disruption and mucosal vasodilation (Holzer *et al.* 1991).

The role of gastric secretions might also be involved in SP control of gastric mucosal protection. It was observed that gastric acid secretion stimulated by insulin, pentagastrin and carbachol was not capsaicin sensitive (Esplugues *et al.* 1990). Controversial effects were obtained with histamine. Soldani *et al.* (1992) observed a significant change in acid secretion after intragastric capsaicin under basal and histamine-stimulated conditions in the dog. Because gastric acid secretion induced by 2-deoxy-D-glucose was inhibited by intragastric capsaicin, the authors concluded that capsaicin-sensitive fibres are involved in the control of vagally-induced gastric acid secretion in the dog (Soldani *et al.* 1992). This suggestion is confirmed by the finding that functional ablation of capsaicin-sensitive sensory neurones increased 2-deoxy-D-glucose-induced gastric mucosal vulnerability as a consequence of acid hypersecretion and hypermotility (Matsumoto *et al.* 1992a). On the other hand, the results of Uchida *et al.* (1991a) demonstrated that capsaicin treatment in rats increased acid secretion. Moreover, histamine-stimulated gastric acid secretion was potentiated by SP (Barashkova *et al.* 1987), which also inhibited basal somatostatin secretion (McIntosh *et al.* 1987), and capsaicin-sensitive afferent nerve degeneration decreased acid secretion in response to histamine (Alfoldi *et al.* 1986). The discrepancies between the results obtained suggest that the problem of the regulatory role of capsaicin-sensitive sensory nerves in gastric acid secretion is poorly understood, but they may play a role in mucosal resistance.

The influence on mucus secretion might also be implicated in the complex protective effect of sensory peptides in the gastric mucosa. This possibility is supported by the findings that the application of SP in the ferret and human trachea enhances the secretion of epithelial glycoprotein-rich fluids (Borson *et al.* 1988) and that capsaicin pretreatment increases the gastric mucus secretion in the antral mucosa (Uchida *et al.*1993). Intragastric application of capsaicin also increases gastroduodenal alkaline secretion which may participate in its protective effects (Takeuchi *et al.* 1991b, 1992a,b,).

Relationship of substance P, prostaglandins and nitric oxide

Further evidence has suggested that chronic capsaicin pretreatment for depleting sensory neuropeptides as well as administration of NG-monomethyl-L-arginine (L-NMMA) for inhibiting endothelium-derived NO formation, did not induce acute mucosal injury (Whittle *et al.* 1990). However, the coadministration of L-NMMA to capsaicin-pretreated rats caused acute dose-dependent mucosal damage which was inhibited by concomitant administration of L-arginine (Whittle *et al.* 1990).

Recent investigation also demonstrated that the capsaicin-mediated reduction of ethanol-induced gastric lesions was reversed in a dose-dependent manner by intravenous injection of N-omega-nitro-L-arginine (L-NNA), a selective blocker of NO synthase (Brzozowski *et al.* 1993). This deleterious effect of L-NNA on gastric mucosa was completely antagonized by L-arginine. Similar results were obtained when the protective effect of CGRP was inhibited after blockade of the nitric oxide system (Lambrecht *et al.* 1993). What is the role of endogenous prostaglandins, the widely accepted cytoprotective agents, in this process?

Some experimental data indicate that protective effects of capsaicin and CGRP on the gastric mucosa are related neither to an increase of eicosanoid formation (Holzer *et al.* 1990b) nor to a blockade of the prostaglandin system (Lambrecht *et al.* 1993).

Further studies using models of 90 % inhibition of prostaglandin formation in the gastric mucosa by indomethacin (5 mg.kg^{-1}) suggested that prostaglandins may be involved in mechanisms of capsaicin-induced gastric mucosal protection. As examples we can enumerate the following findings. Capsaicin-induced increase in gastric mucosal blood flow implicated in gastric mucosal protection was inhibited after pretreatment with indomethacin (Whittle *et al.* 1990, Matsumoto *et al.* 1991, 1992b, Brzozowski *et al.* 1993). This inhibition of gastric mucosal blood flow correlated with the severity of ethanol-induced mucosal damage. Prior administration of indomethacin also diminished luminal pH and HCO_3^- output stimulated by mucosal application of capsaicin (Takeuchi *et al.* 1992a,b). Additionally, capsaicin ablation of sensory nerves increased gastric mucosal vulnerability during 2-deoxy-D-glucose infusion, effect similar to that due to prostaglandin deficiency (Matsumoto *et al.* 1992a).

Taken together, these results indicate that the gastroprotective effect of capsaicin is mediated by an increased release of sensory neuropeptides. These peptidergic mediators augment gastric mucosal blood flow *via* an endothelium-dependent NO system which can be blocked by specific NO synthase inhibitors. Finally, the gastroprotective and hyperaemic effects of capsaicin are at least partly mediated by endogenous prostaglandins. Whether the stimulation of capsaicin-sensitive nerves would either enhance the prostaglandin formation or inversely that these primary afferent neurones are sensitized by endogenous prostaglandins remains to be elucidated.

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