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Discovery and Mechanism of Gastroprotective Action of Capsaicin

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<http://dx.doi.org/10.5772/58684>

1. Introduction

Capsaicin, the hot principle of red peppers or chilli is a favorite spice in culinary practice and therefore its role in gastric ulcerations has been tested since a long time. In early clinical practice studies in this line using intake of pungent pepper flavoured foods resulted in contradictory conclusions and for patients having peptic ulcers intake of hot spicy foods was forbidden (Schneider et al., 1956, Lennard-Jones and Babouris, 1965, Viranuvatti et al., 1972, Solanke, 1973). Furthermore, animal experiments (Sanchez-Palomera 1951, Makara et al., 1965) were neither conclusive. In the latter study aggravation of gastric ulceration in rats was observed by capsaicin application into the stomach while pungent paprika extract in oil inhibited the reserpine-induced gastric ulcerations in the rat. The authors supposed that protective effect of carotenoids in the extract counteracted the ulcerogenic effect of capsaicin (Makara et al 1965).

Studies in our laboratories on the actions of capsaicin in the guinea-pig isolated ileum revealed that capsaicin acting in a highly selective way elicits in low concentration a new type of neural contraction which after higher doses are completely abolished (Barthó and Szolcsányi 1978, Szolcsányi and Barthó 1978). This effect was elicited by neuropeptides as substance P released from the sensory nerve terminals in response to capsaicin. The neuroselective action of capsaicin was shown by its lack of effect on function of cholinergic, adrenergic, purinergic, enteric peptidergic neural responses (Szolcsányi 1984, 1996). These capsaicin-sensitive unorthodox sensory nerve terminals served as nerve endings mediating both afferent sensory and mediator releasing efferent functions. On "capsaicin-sensitive" neural elements the presence of a "capsaicin receptor" was predicted (Szolcsányi and Jancsó-Gábor 1975) which was later cloned (Caterina et al 1997) and is now named as Transient Receptor Potential Vanilloid Type-1 (TRPV1). TRPV1 is a nonselective cation channel gated by long list of

exogenous and endogenous chemical agents including H^+ as well as noxious heat (Jordt et al. 2000, Szolcsányi and Sándor 2012).

The capsaicin-sensitive cutaneous and visceral sense organs correspond to the C- and $A\delta$ – polymodal nociceptor group of primary afferent neurons (Szolcsányi 1996, 2014).

Capsaicin elicits cutaneous enhancement of microcirculation which can be elicited also by antidromic dorsal root stimulation. Antidromic vasodilatation evoked by dorsal root stimulation was known since over a century (Bayliss 1901) but our recent laser-Doppler results revealed that it can be activated at subnoxious level of stimulation applying very low frequency of discharges (0.1 Hz or less). Thus this highly efficient efferent function of these sense organs elicits maximum cutaneous vasodilatation from lower level of stimulation than it causes sensation (Szolcsányi 1996, 2004). These fibers with “sensory-efferent” functions differ from the theoretical so called “nocifensor” nerves of the posterior root system proposed by Sir Thomas Lenis (1937) since he predicted that they have only efferent but no sensory function. (Szolcsányi 2013).

On the basis of our results with the “sensory-efferent” function of TRPV1-expressing “capsaicin-sensitive” sense organs of the skin it was tempting to test whether it could operate also in the stomach mucosa where the acidity of the gastric juice, spicy foods or drugs like acetyl salicylic acid seemed a rational site where this local neuroregulatory vasodilator system might operate and play an important role in gastroprotection. On this ground we started to analyze from the late seventies the effect of blocking or stimulation these capsaicin-sensitive nerve endings on gastric ulcer formation in the rat.

2. First evidence for the gastroprotective role of capsaicin-sensitive nerves

In the first series of experiments on rats (Szolcsányi and Barthó 1981) gastric ulcers were provoked by pylorus ligation (Shay et al 1945) or by acid distension (Gáti and Guth 1976). In rats pretreated with capsaicin (50+100 mg/kg s.c 6-8 days before the experiment) a systemic blockade of capsaicin-sensitive nerve endings was achieved. These rats did not react to capsaicin if it was instilled into the eye and as revealed earlier this state of loss of nociceptive function was coupled with ablation of sensory nerve-mediated neurogenic inflammation (Jancsó et al 1967) or other sensory-efferent responses (Szolcsányi 1996). Fig 1A shows the effect of this capsaicin-induced blockade of sensory nerve endings on gastric ulcer formation in the Shay ulcer model. In the pretreated group mucosal lesions appeared as early as at the 7th hour after pylorus ligation and at the 9th hour deep extensive nearly perforating lesions were observed in the forestomach. On the contrary out of the 20 control rats terminated 7-9 hours after ligation petechial and minimal mucosal lesions appeared only in two animals. At the 14th hour incidence of perforation was only 13% in the control group and 75% in the group of capsaicin-pretreated rats. Differences at 7th, 9th and 14th hours in ulcer indexes of Fig 1A were highly significant ($P < 0.01$; $n=8-11$ of each group).

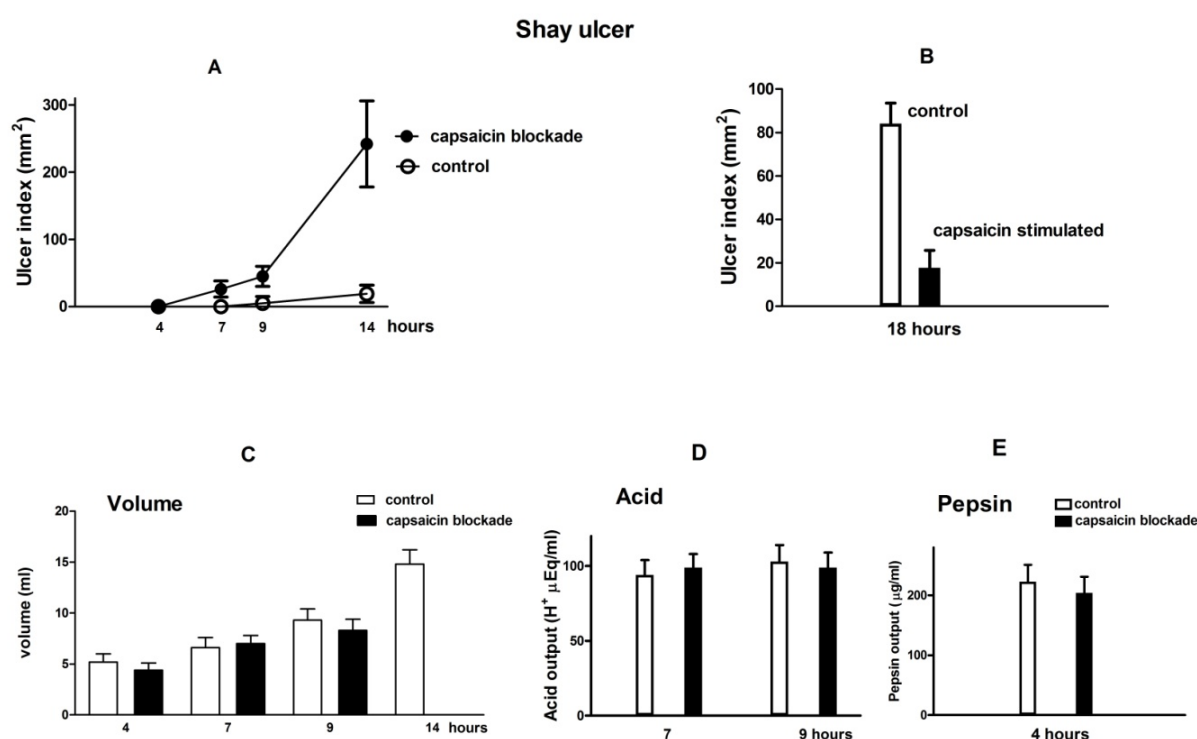


Figure 1. Effect of blockade of capsaicin-sensitive sensory neurons on gastric ulceration in rats evoked by pylorus ligation (A), on volume of gastric juice (C) as well as on gastric acid (D) and pepsin secretion (E) at different time points after pylorus ligation. Gastric ulcers of control rats and that of rats which received by oral application low dose of capsaicin (0.5 μg/0.5 ml and 4 hours later 50 μg/0.5 ml) given into pylorus ligated rats (B).

Aggravation of gastric ulcer formation was not due to enhancement of aggressive factors responsible for mucosal damage. Gastric secretion of the capsaicin pretreated group of animals did not differ from that of the controls as shown on Fig 1C, D and E. The volume, acidity and pepsin concentration of the gastric juice as measured at different time points were similar. Since at the 7th hour petechiae appeared in the capsaicin pretreated group the pepsin concentration was determined only at the 4th hour. Thus it has been concluded that in rats where the function of capsaicin-sensitive nerve endings were abolished in the stomach the gastroprotection is severely impaired against the injurious effect of secreted gastric content inducing H⁺ back-diffusion and distension. This conclusion was supported also in another model when constant acid-distension was used (Gáti and Guth 1976). In these experiments the animals under pentobarbitone anaesthesia (40mg/kg ip) received 0.1M HCl in 6ml/100g volume through the duodenum and thereafter both the esophagus and the duodenum were ligated. The animals were sacrificed one hour later and mucosal lesions of the removed stomach was determined. In 17 control rats the incidence of lesions was 59% and the area of damaged mucosa (ulcer index) was 19±7mm². In 15 rats where the functions of capsaicin-sensitive sensory nerve ending were abolished all rats had mucosal erosions and the gastric ulcer index was 41±11mm² (p<0.002).

On the basis of these remarkable clear results it has been concluded that capsaicin-sensitive nerve endings of the stomach have a gastroprotective effect in peptic ulcer models of the rat.

In another series of experiments it was also revealed, that this gastroprotective sensory-efferent mechanism is enhanced in rats where sensory stimulating low concentration of capsaicin was applied in the Shay model of gastric ulcer. Since it had been shown earlier (Szolcsányi and Jancsó-Gábor 1976) that topical application of capsaicin up to a concentration of 10 µg/ml stimulates the sensory nerve endings in the conjunctiva without causing desensitization this concentration was applied: 5µg capsaicin in 0.5ml was introduced into the stomach after pylorus ligation and 50µg four hours later when the volume of gastric juice was shown to be enhanced to 5ml (Fig 1C). 18 hours after pylorus ligation all control rats had severe forestomach lesions (ulcer index 84.1 ± 9.5), while in the group of rats where low concentration of capsaicin was introduced into the stomach for stimulation of the nerve endings clear gastroprotective effect was observed (ulcer index 17.8 ± 8.0 mm²). The difference between the two groups was highly significant ($p=0.002$).

Threshold concentration of capsaicin on the human tongue which elicits recognizable slight warm sensation is about 0.2µg/ml and a concentration of 1-2µg/ml causes the well known hot spicy sensation (Szolcsányi 1977). Thus, in this range of culinary practice commonly used slightly hot foods capsaicin is gastroprotective and inhibits the development of mucosal erosions. Capsaicin content of pungent chilli pods varies between 0.2-1.4%. Thus, regular intake of very hot foods can produce 1) local desensitization of gastric TRPV1-expressing capsaicin-sensitive sensory nerve endings; 2) enhance vagal reflexes causing smooth muscle contractions and producing gastric discomfort or even pain if gastric ulcers are already present; and 3) induce focal oedema with mucosal inchaemia (Viranuvatti et al 1972) probably mediated by neurogenic inflammation (Jancsó et al 1967, Szolcsányi 1996).

On the basis of the first results and considerations the effect of capsaicin on gastroprotection had been presented in a schematic way as shown on Fig 3. Acid back-diffusion activates both the capsaicin-sensitive sensory nerve endings and release vasodilator mediators from mast cells which enhance mucosal microcirculation and protect the epithelial barrier against erosions which could produce peptic ulcer formation. This natural protective mechanism can be enhanced by low concentration of capsaicin present e.g in spicy flavoured foods. The significance of the capsaicin-sensitive neural part in this protective hyperaemic response is underlined by the fact that if these nerve endings are not functioning under experimental conditions described above severe ulcerations will develop in acid-back diffusion models of gastric ulcers. It is important to note, however, that no erosions in the stomach develop after capsaicin-induced sensory blockade under control conditions. Thus without aggressive factors TRPV1-expressing capsaicin-sensitive nerve endings are not required for gastroprotection.

It is worthy to emphasize, that the mechanism of gastroprotection mediated by subepithelial enhancement of microcirculation clearly differs from the cytoprotection of the epithelial cells described by Robert et al (1979). Cytoprotection is mediated by the release of prostaglandins mainly PGE₂ which inhibit ulcerations induced by tissue damaging necrotic agents (96% ethanol, 0.6M HCl, 0.2 M NaOH, 25% NaCl) which in fact destroy the superficial protective layer of the stomach. Using these aggressive treatments in rats where the capsaicin-sensitive nerve endings were blocked by capsaicin pretreatment no difference in number of lesions, but a significant reduction in the severity of the mucosal damage was observed (Szolcsányi and

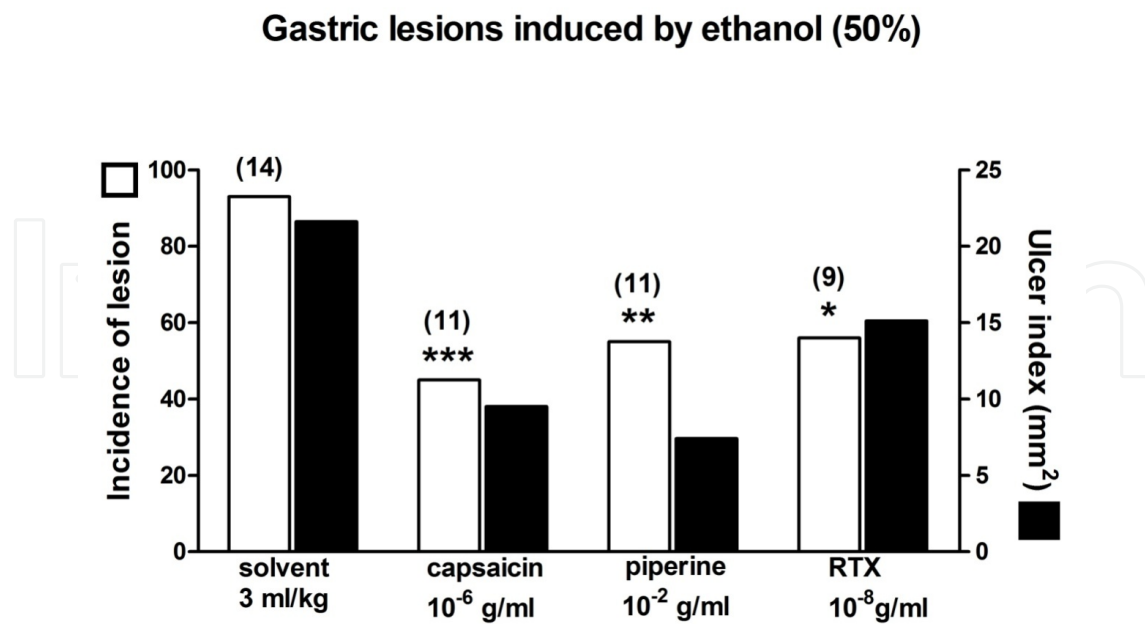


Figure 2. Gastric ulcers of rats induced by ethanol (50%) containing capsaicin, piperine or resiniferatoxin (RTX) in doses indicated. Number of rats in each groups in brackets. Significance ***: $P < 0.01$, ** < 0.02 , * < 0.05 from the values obtained on rats which received ethanol with solvent as control.

Mózsik 1984), just in contrast to the H⁺back-diffusion models discussed earlier. It has been concluded that in this case ulcerations evoked by profound tissue damaging chemical agents resulted in inflammatory reaction and part of it was mediated by the release of substance P (Sharkey et al 1984) released from the capsaicin-sensitive nerve endings (neurogenic inflammation) which are released at higher frequencies of stimulation than the release of CGRP which induces gastroprotective enhancement of microcirculation (Szolcsányi 1996, 2004).

3. Gastroprotection induced by capsaicin-sensitive nerves in animal experiments

Five years after we described the first data and a proposed mechanism for explaining the effect of capsaicin on gastric ulcer formations other groups also supported our results on the gastroprotective effect of capsaicin. Holzer and Sametz (1986) reported that in adult rats treated in the neonatal age by capsaicin which induces a permanent loss of sensory neurons including also a major group of TRPV1 –expressing neurons for ref (Szolcsányi and Pintér 2013) gastric ulcers evoked by indomethacin is aggravated although the release of prostaglandin E₂ remained unchanged. Proposal for the involvement of the adrenals in this capsaicin-sensitive gastroprotective effect in the indomethacin-induced ulceration was raised by another group (Evangelista et al 1986). One year later it has been revealed by immunohistochemistry that in the digestive tract of rats the highest concentration of the potent vasodilator neuropeptide, calcitonin gene-related peptide (CGRP) is present in the stomach (45 ± 2.8 pmol/g wet weight).

After neonatal capsaicin pretreatment the peptide content was reduced by greater than 95% (Sternini et al 1987). Subsequently our data about the gastroprotective effect of intragastric low concentration of capsaicin was supported in case of the ulcerogenic effect of 25% ethanol (Holzer and Lippe 1988). This study provided also evidence against the involvement of autonomic nervous system in the gastroprotective effect of capsaicin and subsequently this group described that intragastric capsaicin (62-640 μ M) had no effect on nonstimulated acid output of the rat stomach and by light and scanning electron microscopy no signs of mucosal damage was observed (Lippe et al 1989). It is worthy to mention here, that in 1988 it was also reported that in humans using videoendoscopy no visible mucosal damage was observed in individuals who have eaten hot Mexican meal with chili but in those subjects who was taken bland meal plus aspirin multiple erosions developed (Graham et al 1988).

Beyond capsaicin other TRPV1 agonists also induced gastroprotection (Szolcsányi 1990). Fig 2 shows that in these experiments 50% ethanol was given through a stomach tube to conscious rats which evoked mucosal lesions in almost all rats as detected one hour after ethanol exposure (first two columns of Fig 2). Capsaicin, piperine, the pungent principle of black pepper and resiniferatoxin (RTX), the highly potent irritant of *Euphorbia resinifera* as TRPV1 agonists (Szállási and Blumberg 1999, Szolcsányi 2004) were dissolved in the ethanol and given to three groups of rats ($n=9-11$). Fig 2 shows that the three TRPV1 agonists given in similar pungent potency ranges induced similar significant gastroprotection against ethanol-induced mucosal ulcerations (Szolcsányi 1990). RTX similarly as capsaicin induces enhanced blood flux of the stomach wall as detected by laser-Doppler flowmetry (Abdel-Salam et al 1996).

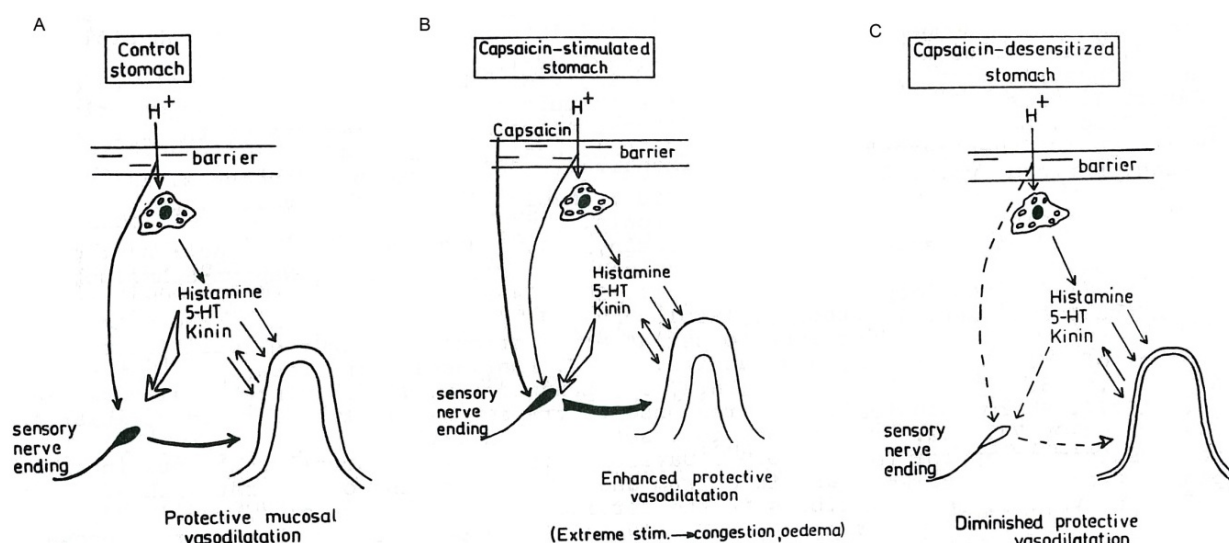


Figure 3. Schematic representation of the hypothetical role of capsaicin-sensitive sensory nerve endings in response to acid distension models which induced gastric mucosal erosions and ulcerations (reproduced from Szolcsányi and Barthó, 1981 with kind permission of the Akadémiai Kiadó, Budapest). A. H⁺ back-diffusion through the epithelial barrier activates both capsaicin-sensitive chemoceptive nerve endings and mast cells which release vasodilator mediators and enhance mucosal microcirculation. B. Low concentration of capsaicin in the stomach enhances the gastroprotective vasodilatation. C. Blockade of capsaicin-sensitive nerve terminals induces depletion of the sensory neuropeptides. In these rats the natural gastroprotective mucosal vasodilatation is impaired.

4. Mechanism of action of gastroprotection of capsaicin

In the defense mechanism to maintain the structural integrity of the gastric mucosa unstirred layer of mucosa-bicarbonate-phospholipid barrier (Fig 4) and the surface epithelial cell layer with tight and gap junctions form the superficial layers of gastroprotection including cytoprotection (Robert et al 1979, Whittle 1993, Abdel-Salam et al. 1999, 2001, Mózsik et al. 2007). Subendothelial enhanced microcirculation proposed to be the main site where capsaicin and TRPV1 agonists (Fig 3) induce the gastroprotective effect was supported by several lines of evidence beyond the opposite effect of capsaicin desensitization on H^+ back-diffusion models and on ulcers provoked by epithelial necrotizing agents suitable to be inhibited by the cytoprotective prostaglandins.

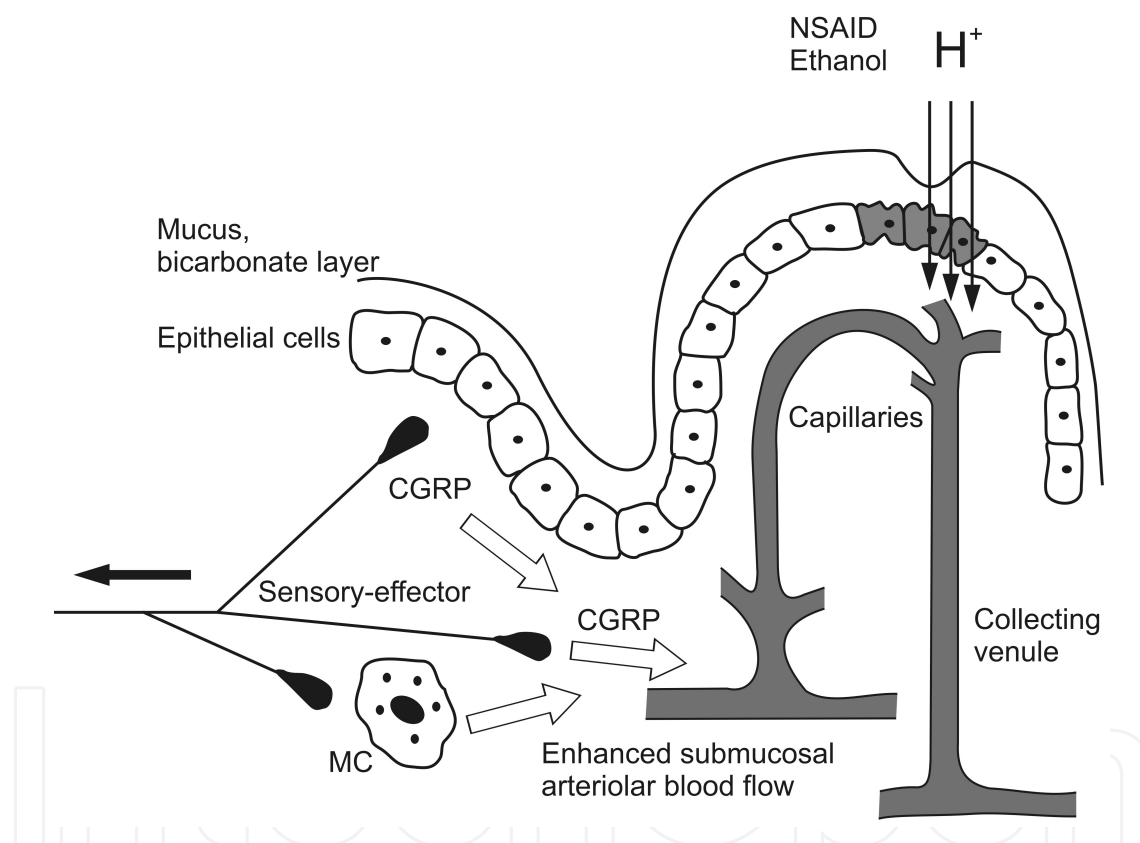


Figure 4. Mechanism of capsaicin-sensitive sensory-effector nerve terminals in gastroprotection depicted on a modified scheme of Whittle (1993). Black arrows: H^+ backflow through the epithelial barrier damaged by nonsteroid anti-inflammatory drugs (NSAID), ethanol or other aggressive agents. White arrows release of CGRP from capsaicin-sensitive nerve endings or other vasodilator mediators released during degranulation of mast cells (MC). The released mediators induce enhancement of mucosal microcirculation. Thick black arrow: action potentials of sensory message to the central nervous system.

TRPV1 is a non-selective cation channel with preferential gating to Ca^{++} over Na^+ (Caterina 1997, Szolcsányi and Sándor 2012) and there is firm evidence in the skin that both CGRP and TRPV1 are coexpressed in the sensory receptors terminating in the epidermis (for ref see Szolcsányi and Pintér 2013). Furthermore it has been shown that in vitro no inhibition of

sensory neuropeptide release ensues in the presence of blockade of axon reflexes by tetrodotoxin or lignocaine (for review Szolcsányi 1996, 2013).

Thus CGRP is released from the sensory nerve ending which in an unorthodox way serves in a bidirectional neuroregulatory sensory-efferent function. Nevertheless, capsaicin prevented deep but not epithelial mucosal damage and local intra-arterial infusion of tetrodotoxin prevented the capsaicin-induced gastroprotection (Holzer et al 1991). These results indicate, that if the stomach mucosa was perfused with capsaicin in 25% ethanol nerve terminals excite the superficial layers and evoke axon reflexes (Fig 4). In this case mainly those sensory nerve endings situated deeper near to the vessels are activated through branching axon collaterals and mediators released by Ca^{++} influx through the TRPV1 channel in the subepithelial sensory nerve endings play a minor role in enhancement of mucosal microcirculation. There is, however, no evidence to suppose that in axon reflex arrangement in the periphery some nerve endings of primary sensory neurons might have nerve terminals specialized for efferent, mediator releasing function in antidromic vasodilation (Szolcsányi 1996, 2013).

Recently another hypothesis for gastroprotection (Holzer and Maggi 1988), in fact a revival of Lewis's "nocifensor" fiber theory was raised according to which vasodilator mediators are released from nerve endings of capsaicin-sensitive DRG fibers which have only efferent function without mediating messages to the central nervous system. In other words these authors in this paper proposed that peripheral release of neuropeptides in the stomach mucosa takes place from effector nerve terminals of a subset of DRG neurons which have only efferent function. They showed that acid challenge of the mucosa elicited rapid c-fos mRNA activation in the nucleus tractus solitarius but not in the spinal cord, while capsaicin-induced mucosal vasodilation was abolished by splanchnic nerve denervation but remained intact after vagotomy. (Holzer and Maggi 1998). Subsequent data (Blackshaw et al 2000) indicated that most of the vagal afferents excited by low pH are capsaicin-insensitive fibers from where neuropeptides are not released (Szolcsányi 2004). Thus they could mediate the c-fos activation in the nucleus tractus solitarius. It has been shown earlier that for release of sensory neuropeptides a very low frequency of activity is already maximal (see Introduction and Szolcsányi 1996 2013). Therefore pronounced mucosal vasodilatation without c-fos activation can be evoked (Szolcsányi and Barthó 2001). More recent data of Peter Holzer's group seems to support our conclusion, since the lack of c-fos activation in the dorsal half of the spinal cord by mucosal HCl application was in contrast to the effect of capsaicin which evoked c-fos activation both in the nucleus tractus solitarius and particularly in the lamina I of dorsal horn of the spinal cord (Holzer et al 2005). Distension of the stomach enhanced c-fos expression and CGRP expression both in the spinal cord and medulla oblongata (Zhang et al 2006).

The pivotal role of CGRP in gastroprotection due to an enhancement of mucosal microcirculation (Peskar et al 1993) in response to stimulation of peptidergic capsaicin-sensitive vagal and spinal sensory neurons are supported by several further lines of evidence. Gastric hyperemia to intragastric capsaicin or acid back diffusion (0.15M HCl +15% ethanol) was blocked by the CGRP antagonist hCGRP 8-37 (Li et al 1991, 1992). Some data indicate that beyond the vascular effect of CGRP it induces also release of somatostatin (Inui et al 1991). Furthermore a subpopulation of capsaicin-sensitive vagal sensory neurons contain also

somatostatin which is released by electrical nerve stimulation of the nerves both from the thoracic and abdominal parts of the nerves (Than et al 2000).

Recently it has been shown, that TRPV₁ and neuronal nitric oxide synthase (nNOS) are coexpressed in sensory fibers around the vessels of the gastric mucosa and the capsaicin-induced enhancement of mucosal blood flow appeared to be diminished by nNOS inhibition (Raimara et al 2013). Epidermal growth factor (EGF) reduces gastric mucosal lesions evoked by ethanol by activating capsaicin-sensitive sensory nerve terminals (Matsumoto et al 2001).

The role of prostaglandin E₂ and its receptors EP1 in cytoprotection against necrotizing agents is well established and has been discussed to be different from the effects of capsaicin. Recent data using EP1 and prostacyclin (IP) knockout mice showed that capsaicin-induced gastroprotection is present in gene-deleted mice of EP1 but disappeared in IP knockout mice (Takeuchi, 2014). The role of prostacyclin in capsaicin-induced gastroprotection seems to be interesting for further research. For further reviews see Abdel-Salam 2001, Pawlik et al 2001, Evangelista 2009, Mózsik et al 2007, 2014, Luo et al 2013).

It is important to note that stimulation of capsaicin-sensitive perivascular nerve terminals in vitro elicits slow inhibitory junction potential (IJP) and dilator response on mesenteric smooth muscle cells. IJP evoked by capsaicin or electrical stimulation was unaffected by endothelial removal or pharmacological blockade of autonomic neuroeffector mechanism by pharmacological treatments with guanethidine, 6-hydroxydopamine, propranolol, atropine, α , β -methylene ATP (Meehan et al. 1991).

The role of mast cells in gastric mucosal injury evoked by H⁺back-diffusion, NSAID, ethanol and other aggressive chemicals has been described since a long time (Fig 3, 4) (Szolcsányi and Barthó 1981, Takeuchi et al 1997, Rydning et al. 2004). Recently it has been reported, that mast cell deficient Sash mice are highly susceptible to piroxicam-induced gastric ulceration. Thus, it seems that beyond the potent gastroprotective effect of capsaicin-sensitive nerve endings described earlier and presented in humans (Mózsik et al., 2014 in this volume) mast cells play also role through releasing vasodilator mediators (Rydning et al., 2002), but by releasing histamine it enhances on H₂ receptors gastric acid secretion which in these mice did not interfere with the ulcer formation (Hampton and Hale, 2013).

5. Conclusions

CGRP release from the capsaicin-sensitive TRPV1-expressing sensory nerve endings induces potent enhancement of submucosal microcirculation which results in marked gastroprotective effect. CGRP, substance P and somatostatin are released from these nerve endings which by arborizations could induce effector tissue responses also by axon reflexes.

Capsaicin-sensitive sensory nerve-mediated vasodilation together with mast cell degranulation participate in the gastroprotective effect against mucosal injuries induced by aggressive agents as H⁺back-diffusion, ethanol or nonsteroid anti-inflammatory drugs (NSAID) and provide therapeutic means for gastroprotection.

Acknowledgements

I thank Ágnes Kemény and Éva Szőke for drawing the figures and Brigitta Incze for typing the text. The work was supported by the grant SROP U.2.2.A-11/1/KONV-2012-0024.

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