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Approach to Role of Capsaicin - Sensitive Afferent Nerves in the Development and Healing in Patients with Chronic Gastritis

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1. Introduction

The intact gastrointestinal mucosa can be kept as good equilibrium between the aggressive and defensive factors. These factors have not been fully discovered, however the main aggressive factors are well defined. Gastritis is defined as a pathomorphological appearance of inflammation in the gastric mucosa. Gastritis may be caused by different factors such as *Helicobacter pylori* (*H. pylori*), bacterial overgrowth in a hypochlorohydric stomach, autoimmune mechanisms or chemical agents such as short and long-term nonsteroidal anti-inflammatory drug therapy.

The possible physiological, pathological and pharmacological role(s) of afferent nerves has (have) not been analyzed just recent studies search on its most important role(s) in GI physiology, pathology and pharmacology. Our attention has been focused on capsaicin-sensitive afferent nerves during the last decades.

The possible roles of the capsaicin-sensitive afferent nerves have been approached to gastrointestinal tract from the years of 1980 by our work-team in animal experiments, in healthy human subjects with histological intact and in patients with different disorders (Mózsik et al., 1997, 2001, 2005a, 2007). Capsaicin (given it in small doses) protected the gastrointestinal mucosal damage induced by different necrotizing agents (such as physical, chemical, drugs, etc.) in animal experiments and in human healthy subjects, in patients with different gastrointestinal disorders (Mózsik et al., 1997, 2005a, 2007, 2009). The functional state of some part of afferent nerves (capsaicin-sensitive afferent nerves) can be modified by application of capsaicin by a dose-dependent process (capsaicin, given in small doses stimulates, meanwhile given in higher dose produces reversible and irreversible inhibition or impairment) (Szolcsányi et al., 1984a; Mózsik et al., 2001).

1.1 Aims of observations

The aims of our observations were:

To study the distribution of capsaicin receptor (TRVP1), calcitonin gene-related peptide (CGRP) and substance P (SP) in the human gastric mucosa in histologically intact with functional dyspepsia, chronic gastritis (diagnosed histologically);

To evaluate the possible role of capsaicin-sensitive afferent nerves in the development of gastritis produced by *H. pylori*;

To analyse the role of capsaicin afferent nerves (e.g. immunohistochemical distribution of TRVP1, CGRP, SP) in the the gastric mucosa of the same patients with chronic gastritis produced by *H. pylori* before and after eradication treatment;

To approach the possible gastric mucosal defensive mechanisms of capsaicin-sensitive afferent nerves (immunohistochemical distribution of TRVP1, CGRP, SP) in the development of gastritis and its treatment;

To demonstrate a new pathway (namely the possible productions of new chemical compounds acting on the capsaicin-sensitive afferent nerves) to introduce (as one of the possibilities) in the treatment of chronic gastritis.

1.2 Patients and methods

The patients with symptoms suffering from functional complaints (n=40), chronic gastritis with *H. pylori* negative (gastric discomfort sensation, nausea, loss of appetite, vomiting) (n=30) and *H. pylori* positive (n=39) infection. The age of patients was between 39 to 68 years, and these patients were near to be equal to males and females.

Gastric biopsies were collected from the hyperaemic areas of the corpus and antrum of the stomach by oesophago-gastroscopy. The *H. pylori* infection was detected using the ¹⁴C urea breath test (¹⁴C UBT), the rapid urease test, and specific histological examinations. The gastric tissue samples were classified into the different groups of chronic gastritis to the updated Sydney system by an independent histopathologist (Dömötör et al., 2007, Lakner et al., 2010).

The immunohistochemical studies were carried out on formalin fixed, paraffin embedded tissue samples using anti-TRVP1 receptor, anti-SP and anti-CGRP antibodies.

18 patients with *H. pylori* positive chronic gastritis went over the same physical, laboratory, ultrasonographic, endoscopic and histological examinations (mentioned above) before and after eradication treatment.

1.3 Results

Distribution of TRVP1 positive (20%) and negative (80%), CGRP positive (30%) and negative (70%), SP weak (75) and strong (25%) in gastric mucosa of healthy human subjects. TRVP1 positive 82%, and negative 18%, CGRP positive 80% and negative 20%, SP weak 85% and strong 15% in patients with *H. pylori* positive chronic gastritis. TRVP1 positive 70% and negative 30%, CGRP positive 63% and negative 37%, SP weak 59% and strong 28% in patients with *H. pylori* negative chronic gastritis.

The eradication treatment for *H. pylori* infection was successful (in 16 from 18, 89%) and complaints (epigastric pain, heart burn, abdominal expansion) also decreased. Histologically healthy gastric mucosa could be detected only in 22% (4 from 18) and appearance of gastric mucosa (just in moderate histological picture) was obtained.

TRVP1 positive 89% and negative 11%, CGRP positive 100%, SP positive 6% and negative 94% in patients with *H. pylori* positive gastritis, before eradication treatment. TRVP1 positive 72% and negative 18%, CGRP positive 100%, SP negative 100% in patients with *H. pylori* positive chronic gastritis after classical eradication treatment.

1.4 Main conclusions

H. pylori does not represent an exclusive factor for the development of chronic gastritis in patients. The many other compounds (physical, chemical agents) are able also to produce chronic gastritis in patients.

The expression of TRVP1 and increased CGRP participated in the development of chronic gastritis (without and with *H. pylori* infection), meanwhile the SP probably does not participate in this process. These results clearly indicate that the histological picture of chronic gastritis is independent from the presence of commonly emphasized role of *H. pylori* infection in patients, and much more complicated series of mechanisms are present in the development of human chronic gastritis (as we now suggest those at this time).

The classical eradication human therapy does not modify the immunohistological distribution of TRVP1, CGRP and SP in the human gastric mucosa with *H. pylori* infection. Many animal and human observations indicated that the stimulation of capsaicin-sensitive afferent nerves by application by small doses of capsaicin (or other compounds) produced defensive effects against the different physical, chemical, bacteriological, immunological agents.

The capsaicin-sensitive afferentation (s) has (have) a permanent defensive role(s) against gastric mucosal damage by different noxious agents, in the human gastric mucosa. The innovative pharmacological research may offer a new pathway to prevent the gastric mucosa induced by different agents (including the *H. pylori* infection).

2. Introduction

The principle role of efferent vagal nerves has been emphasized in the development of gastrointestinal mucosal damage and prevention, as well as in medical treatment involving anticholinergic agents, histamine H₂ receptor inhibitors, proton pump inhibitors during the last century. From the initial observation of capsaicin desensitization phenomenon, a long-lasting chemoanalgesia and impairment of thermoregulation in the 1970s, chain of new discoveries led to the discovery of the capsaicin receptor, a type of C-polymodal nociceptors (Szolcsányi, 2004b). The effects of capsaicin depend on the applied doses and duration of exposure (Mózsik et al., 2001; Szolcsányi, 2004a). These different effects of capsaicin are: (1) excitation; (2) sensory-blocking effect; (3) long-term selective neurotoxic impairment and (4) irreversible cell destruction.

Neurogenic inflammation is mediated by these C-afferents, which are supplied by the putative capsaicin receptor. These afferents are called capsaicin-sensitive chemoreceptive afferents. They opened new avenues of local peptidegic regulation in peripheral tissues. It has been suggested that, in contrast to classical axon theory, capsaicin-sensitive sensory system has a dual sensory-afferent function, whereby initiation of afferent signals and neuropeptide release are coupled at the same nerve endings. Furthermore, for instance in the skin at threshold stimuli which do not evoke sensation already maximum efferent response as enhanced microcirculation is elicited. Recently, the capsaicin receptor has been cloned and named as transient receptor potential vanilloid-1 (TRVP1) (Caterina et al., 1997). TRPV1 was detected in the area postrema and in the nucleus tractus solitarii where the afferent fibres of the vagal nerve come to an end. Studies with capsaicin receptor led to discovery of the first temperature-gated ion channel gated by noxious heat, protons, vanilloids and endogenous ligands as anandamide, N-oleodopamine and lipoxygenase products. Another recent achievement was the discovery of a novel neurohormonal regulatory mechanisms mediated by somatostatin. Somatostatin released from the TRVP1-expressing nerve endings reaches the circulation and elicits anti-inflammatory and analgetic sensory functions (Szolcsányi, 2004; Helyes et al., 2004).

The vagal nerve contains also only 10% efferent and 90% of afferent nerve fibres, and 9% of these afferent fibres are the capsaicin-sensitive afferent nerves (Gabella & Pease, 1973;

Grijalva & Novin, 1990). Thus, the amount of the efferent nerves and the capsaicin-sensitive afferent nerves are roughly the same amount in the vagal nerve.

The possible role of afferent vagal nerve was studied in the last decades both in development of gastrointestinal mucosal damage and protection (Mózsik et al., 1997; 2004a; Holzer, 1999; Abdel-Salam et al., 1999). Recently, the gastroprotective effect of capsaicin against chemical agents (ethanol, indomethacin) has been proven in human healthy subjects (Mózsik et al., 2004b, 2005). The beneficial effect of capsaicin has also been shown in patients with functional gastrointestinal disorders (Bartolotti et al. 2002; Bhat & Bielefeldt, 2006).

The integrity of gastric mucosa is an equilibrium state between aggressive and defensive factors. The loss of this balance leads to the development of most gastric disorders, like gastric mucosal ulceration and most likely chronic gastritis.

One of the aggressive factors is *H. pylori* infection, which is a wide spread bacteria, one of the commonest pathogen bacillus in humans (Hocker & Hohenberger, 2003). At least half of the world's population could be infected with this organism (Logan & Walker, 2001). *H. pylori* - as a causative factor - increases the risk for development of human gastrointestinal disorders such as acute gastritis, chronic gastritis, gastric ulcer, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, gastric adenocarcinoma, duodenal ulcer and it may be implicated in iron deficiency anemia and also in extra-gastrointestinal disorders (ischemic heart disease, ischemic cerebrovascular disease, atherosclerosis etc) (Parsonet, 1995; Peng et al., 1998; Pakodi et al., 2003; Mitani et al., 2004; Janulaityte-Gunther et al., 2005; Salih et al., 2005; Zhang et al., 2005a). The eradication of this organism has generally been associated with histological improvement of gastritis (Salih et al., 2005).

On the other hand, one of the defensive mechanisms is the capsaicin-sensitive afferentation. During administration of small doses of capsaicin (from ng/kg to µg/kg body weight) neurotransmitters such as substance-P (SP), calcitonin-gene related peptide (CGRP) and somatostatin (SS) are released from this nerve endings (Holzer, 1998, 1999; Szolcsányi, 2004). These mediators can increase mucosal blood flow by vasodilatation (Holzer et al., 1991), can activate mast cells and immunocells in the mucosa (Stead, 1992), and somatostatin can elicit systemic anti-inflammatory and analgetic "sensory functions". The immunodistribution of neuropeptides (SP, VIP, NPY, SOM, GAL, and TH) released from the sensory neurons and their neuroimmune function are known in *H. pylori* positive gastritis, but not have been examined in gastritis without *H. pylori* infection (Sipos et al., 2006).

The presence of this receptor and released neurotransmitters could be studied in the development of human gastrointestinal disorders including gastritis, peptic ulcer, polyp without and with dysplasia, tumour and inflammatory bowel diseases by immunohistological method (Kihara et al., 2003; Zhang et al., 2005b; Dömötör et al., 2005; Mózsik et al., 2007). In our further research significant changes were observed in the immunohistological distribution of TRPV1, CGRP and SP in patients with chronic *H. pylori* positive gastritis and in histological healthy subjects but no change could be detected between the patients suffered from chronic gastritis without or with *H. pylori* infection (Dömötör et al., 2006). The effect of omeprazole and omeprazole-like compounds could also be demonstrated in the gastric mucosa of rats by the changes of the TRPV1, CGRP and SP immunodistribution and by the reduction of number and severity of gastric mucosal lesions (Mózsik et al., 2005b).

3. Materials and methods

The symptoms of patients suffering from chronic gastritis with or without *H. pylori* infection (21 *H. pylori* positive, 30 *H. pylori* negative) were nonspecific (gastric discomfort

sensation, nausea, loss of appetite, vomiting). The patients underwent physical, laboratory, ultrasonographic, endoscopic and histological examinations at the First Department of Medicine, Medical and Health Centre, University of Pécs, Hungary (Table 1). Twenty people with functional dyspepsia (all of them underwent the aforementioned medical, laboratory, iconographic, and histological examinations and all of these examinations indicated absolutely negative results) were taken as healthy controls. The age of patients was 39 to 68 years; there were 22 males and 29 females with chronic gastritis and 10 males and 10 females in the functional dyspepsia group (Table 1).

Patients:	127 patients, age: 21 – 84 years (68 males, 59 females) Preliminary study by Dömötör et al, 2005
Study 1:	51 patients with chronic gastritis age: 39 – 68 years (22 males, 29 females) 21 <i>H. pylori</i> positive, 30 <i>H. pylori</i> negative 20 persons with functional dyspepsia (controls) age: 41 – 67 years (mean: 52,1 years) (10 males, 10 females)
Study 2:	18 patients with <i>H. pylori</i> positive chronic gastritis (6 males, 12 females) age: 39 – 68 years (mean: 56.4 years) 20 with functional dyspepsia (controls) age: 41 – 67 years (mean: 52,1 years) (10 males, 10 females)

Table 1. Study design. The immunhistological studies for capsaicin-sensitive sensory nerves were carried out on biopsy specimens of gastric mucosa obtained from patients.

Eighteen patients with *H. pylori* positive chronic gastritis went over physical, laboratory, ultrasonographic, endoscopic and histological examinations at the Department of Medicine and Gastroenterology, Markusovszky Teaching Hospital, Szombathely (Hungary). The age of patients (6 males, 12 females) was 39 to 68 years (mean=56,4 yrs). The symptoms of the patients were measured with the same questionnaire. These patient received eradication therapy involving a seven days treatment with double dose proton-pump inhibitor (PPI; pantoprazole 2x40 mg/ day), amoxycillin (1000 mg twice daily) and clarithromycin (500 mg twice daily) according to the actual European guidelines (Malfertheiner et al., 2007). After the first week, the patients medicated normal dose of PPI for another week (Table 1). Six weeks after eradication therapy these patients underwent second gastroscopy with gastric biopsy. Gastric biopsies were collected from hyperaemic areas of the corpus and antrum of the stomach by gastroscopy. *H. pylori* infection was detected using the ¹⁴C UBT, the rapid urease test and specific histological examinations (Warthin-Starry silver staining). Gastric tissue samples were analyzed at the Department of Pathology and classified into different groups of chronic gastritis according to the updated Sydney system (Prince, 1991). The biopsies showed moderate and severe activity of inflammation. Gastric biopsies of patients with chronic gastritis and histologically healthy people were classified into groups by an independent pathologist.

Immunohistological studies were carried out on formalin-fixed, paraffin-embedded tissue samples using the peroxidase-labelled polymer method (Lab Vision Corp., USA). SP was detected by the NC1/34HL rat monoclonal antibody and TRPV1 receptor and CGRP were labelled using polyclonal rabbit antibody (all from Abcam Ltd., Cambridge, UK) (Table 2).

Antiserum	Abbreviation	Species	Dilution	Source
Transient receptor potential vanilloid 1	TRVP1	Rabbit	1:400	Abcam, Cambridge, UK
Calcitonin gene-related peptide	CGRP	Rabbit	1:200	Abcam
Substance P	SP	Rat	1:200	Abcam

Table 2. Antibodies used as primary.

Immunohistochemical analysis was assessed by light microscopy (Olympus). TRPV1 and CGRP were detected as positive or negative, while the immunohistochemical distribution of SP was characterized using the "SP index." This index was calculated by counting immunopositive spots in at least five high-magnification fields. For fields without immunostaining, the score was 0; for fields containing only one positive spot, the score was 1; and for fields with two or more stained elements, the score was 2. The total score in one specimen was divided by the number of scanned fields to obtain the SP index. Based on these results, biopsies were classed into three categories: weak, medium, and strong (Table 3).

SP evaluation	SP index
Weak	<0.5
Medium	≥ 0.5 but < 1
Strong	≥ 1

Table 3. Semiquantitative quantitation of immunohistochemical SP staining in gastric mucosa of healthy subjects and patients with chronic gastritis

Observations were carried out according to Good Clinical Practice (GCP). Human examinations were carried out from 1997 to 2010 and were permitted by the Regional Ethical Committee of University of Pécs, Hungary. Written informed consent was obtained from all participants.

TRPV1 and CGRP were statistically evaluated by chi-square probe, while SP results were semi-quantitatively evaluated by Mann-Whitney's U test. The results were taken to be significant at P values of < 0.05.

4. Results

Results are presented as the typical pictures of the immunomorphological appearance of the studied receptor and mediators in the gastric mucosa in healthy human subjects and in patients with chronic gastritis with or without *H. pylori* infection (Figs. 1-4).

The immunohistochemical results are summarized in Table 4. showing the SP scores (mean $\pm$ SE) in healthy persons and in patients with *H. pylori* positive and negative chronic gastritis. In TRPV1-positive cases of chronic gastritis with or without *H. pylori* infection and in healthy subjects, immunostaining was detected as fine granular cytoplasmic immunosigns in epithelial cells in the gastric mucosa (Fig. 2). TRPV1-positive cases of chronic gastritis were significantly more frequent ($p<0.01$) than in controls, while no significant difference was detected in immunomorphology of TRPV1 between patients with *H. pylori* negative and those with *H. pylori* positive chronic gastritis.

Fig. 1. Immunohistochemical distribution of TRPV1, CGRP and SP in mucosa of the stomach. Arrows show the immunosigns in the epithelial layer of the gastric mucosa (original magnification: 100x).

Fig. 2. Immunodistribution of TRPV1 in the gastric mucosa of a healthy subject (A) and of patient with *H. pylori* negative (B) and *H. pylori* positive (C) chronic gastritis. Arrows show the immunosigns in the epithelial layer of the gastric mucosa (original magnification: 100x).

The characteristic immunodistribution of CGRP was as a fine granular cytoplasmatic positivity in epithelial cells in the gastric mucosa of patients with chronic gastritis with or without *H. pylori* infection and in healthy persons (Fig. 3). Regarding the immunohistological distribution of CGRP, significant differences were observed between healthy controls and *H. pylori* negative chronic gastritis ($p<0.01$) and no significant difference was found between the two types (*H. pylori* negative and positive) of chronic gastritis. Although the number of the positive tissue samples increased in *H. pylori* positive gastritis, it did not reach a significantly different level compared to healthy controls.

Before *H. pylori* eradication, the symptoms of the patients with *H. pylori* positive chronic gastritis were unspecific, epigastric pain (14/18; 77%), heart burn (13/18; 72%), nausea/vomiting (9/18; 50%) abdominal expansion (9/18; 50%), constipation (6/18; 38%). The gastric biopsies of patients with *H. pylori* positive chronic gastritis before eradication indicated moderate and severe activity of inflammation during the regular/common histopathological examinations. The *H. pylori* eradication therapy was successful in 16 from 18 patients (89%) (Figs. 5 and 6). The symptoms were moderated in seven patients (7/18; 39%) and 11 patients (11/18; 61%) had no complaints after eradication treatment.

The immunomorphology of SP was detected as small granular spot-like signals along the mucosal blood vessels in gastric mucosa of healthy subjects and of patients with chronic gastritis with or without the presence of *H. pylori* infection (Fig. 4). No significant difference was observed in the number of low and high SP scores between healthy subjects and patients with chronic gastritis, while medium SP immunohistological samples appeared in *H. pylori* negative and positive chronic gastritis.

The gastroscopy with gastric biopsy was carried out in all patients after *H. pylori* eradication. Histologically healthy gastric mucosa could be detected only in 4 (4/18; 22 %) of the control biopsies and in 14 (14/18; 78%) patients the appearance of chronic gastritis (just in moderate histological picture).

Fig. 3. Immunodistribution of CGRP in gastric mucosa of a healthy subject (A), of patient with *H. pylori* negative (B) and *H. pylori* positive (C) chronic gastritis. Arrows show the immunosigns in the epithelial layer of the gastric mucosa (original magnification: 100x).

Fig. 4. Immunodistribution of SP in gastric mucosa of a healthy subject (A) and of patient with *H. pylori* negative (B) *H. pylori* positive (C) chronic gastritis (original magnification: 100x).

	TRVP1		CGRP		SP			
	+	–	+	–	–	Weak	Medium	Strong
Healthy (n=20)	20%	80%	30%	70%	0	75%	0	25%
<i>H. pylori</i> positive (n=21)	82%	18%	80%	20%	0	85%	0	15%
<i>H. pylori</i> negative (n=30)	70%	30%	73%	27%	0	70%	0	30%
<i>H. pylori</i> positive before eradication (n=18)	89%	11%	100%	0	94%	0	6%	0
<i>H. pylori</i> positive after eradication (n=18)	72%	18%	100%	0	100%	0	0	0

Table 4. Result of immunohistochemistry examinations for TRVP1, CGRP and SP in gastric mucosa of healthy subjects (n=40), patients with *H. pylori* negative chronic gastritis (n=30) and *H. pylori* positive chronic gastritis (n=18) before and after eradication therapy.

Fig. 5. The efficacy of the traditional *H. pylori* eradication treatment in patients with chronic gastritis (n=18) measured by urea breath test.

The TRPV1 was positive in 20% (5/20) in the healthy subjects, that value was 89 % (16/18; $p < 0.001$) before and 72% (13/18; $p < 0.03$) after eradication therapy in patients with chronic *H. pylori* positive patients.

Immunohistochemistry of CGRP was positive in 100% (18/18; $p < 0.001$) of patients before and after eradication (18/18; $p < 0.001$). The SP immunostaing was positive in 25% of control persons (20/20), and in 5.5 % (1/18; $p > 0.05$) before and in 0% (0/18; $p > 0.05$) after eradication. The results of the immunohistological examinations are characterized by the typical histological pictures of the TRPV1 receptor and the mediators (CGRP and SP) and are summarized in Tables 5 and 6.

Fig. 6. Presence of histological inflammation in gastric mucosa of patients with chronic gastritis after classical *H. pylori* eradication therapy treatment (n=18).

TRVP1	Healthy subjects	vs.	<i>H.p.</i> - (+)	↑	p<0.0001	
		vs.	<i>H.p.</i> +	↑	p<0.0001	before eradication
		vs.	<i>H.p.</i> +	↑	p<0.0001	after eradication
CGRP	Healthy subjects	vs.	<i>H.p.</i> - (+)	↑	p<0.0001	
		vs.	<i>H.p.</i> +	↑	p<0.0001	before eradication
		vs.	<i>H.p.</i> +	↑	p<0.0001	after eradication
SP	Weak (strong)	vs.	<i>H.p.</i> - (+)		p>0.005	
		vs.	<i>H.p.</i> +	↑	p<0.0001	before eradication
		vs.	<i>H.p.</i> +	↑	p<0.0001	after eradication

p values were calculated between the identical results obtained in healthy subjects (n=40), in patients with *H. pylori* negative (n=30) and *H. pylori* positive chronic gastritis before (n=18) and after (n=18) eradication therapy.
↑ means increase.

Table 5. Summary of differences in result obtained in immunohistochemistry examinations for TRVP1, cGRP and SP in gastric mucosa of healthy subjects (n=40), patients with *H. pylori* negative chronic gastritis (n=30) and *H. pylori* positive chronic gastritis (n=18) before and after eradication therapy.

5. Discussion

The possible role(s) of the capsaicin-sensitive afferent vagal nerve has been studied by our work-team since the 1980s under physiological and different pathological conditions in animal experiments (Mózsik et al, 1997, 2001, 2004b; Abdel Salam et al., 1999), healthy subjects (Mózsik et al., 2004b, 2005a) and in patients with different gastrointestinal disorders (Dömötör et al., 2005, Mózsik et al., 2006, 2007).

The distribution of TRVP1, CGRP significantly increased in *H. pylori* positive chronic gastritis (in comparison with their distribution in gastric mucosa of healthy subjects), which data suggests that the TRPV1 and CGRP are involved in the development of human chronic gastritis (Tables 6 and 7). However, no significant changes were obtained before vs. after classical eradication treatment in patients with *H. pylori* positive chronic gastritis (Table 8). The SP decreased in patients with *H. pylori* chronic gastritis and its value unchanged before and after eradication treatment.

Histologically healthy gastric mucosa could be detected only 4 (4/18; 22%) *H. pylori* positive patients chronic gastritis at 6 weeks after classical eradication treatment. It was interesting to note, that the distribution of gastric mucosal TRPV1, CGRP and SP did not change in the *H. pylori* positive gastritis before and after classical eradication treatment.

How can we explain these unchanged immunodistribution in the gastric mucosa of *H. pylori* positive gastric chronic gastritis before and after eradication treatment?

We have to start from basic observed facts: 1. TRPV1, CGRP and SP can be immunohistologically detected in the rat and human gastric mucosa under healthy and different pathological circumstances; 2. the changes in expression of TRPV1, CGRP and SP are consequence of activation in the capsaicin-sensitive afferent nerves; 3. the *H. pylori* positivity was proven in all patients with chronic gastritis; 4. the eradication of *H. pylori* was successfully carried out, that associated with significant decrease of patients' complaints; 5. the gastric mucosa became to be negative (intact gastric mucosa) in 25%, and 75% of patients

indicate moderate histological signs of gastritis after eradication treatment; 6. independently from that the exact proof, the chronic gastritis is in association with *H. pylori* positivity, the histological picture of gastric mucosa indicates only a moderate remission.

	TRVP1 positive	TRVP1 negative
Healthy subjects (n=20)	20%	80%
<i>H. pylori</i> neg/pos gastritis (n=51)	↑ (p<0.001)	↓ (p<0.001)
<i>H. pylori</i> pos gastritis (n=18)		
Before eradication	↑ (p<0.001)	↓ (p<0.001)
After eradication	↑ (p<0.001)	↓ (p<0.001)
	NS	NS

↑ means increase. ↓ means decrease. NS means no significant difference. pos means positive. neg means negative.

Table 6. Summary of result obtained in immunohistochemistry examinations for TRVP1 in gastric mucosa of healthy subjects and patients with *H. pylori* negative chronic gastritis (n=30) and *H. pylori* positive chronic gastritis before and after eradication therapy (n=18).

	CGRP positive	CGPR negative
Healthy subjects (n=20)	30%	70%
<i>H. pylori</i> neg/pos gastritis (n=51)	↑ (p<0.001)	↓ (p<0.001)
<i>H. pylori</i> pos gastritis (n=18)		
Before eradication	↑ (p<0.001)	↓ (p<0.001)
After eradication	↑ (p<0.001)	↓ (p<0.001)
	NS	NS

↑ means increase. ↓ means decrease. NS means no significant difference. pos means positive. neg means negative.

Table 7. Summary of result obtained in immunohistochemistry examinations for CGRP in gastric mucosa of healthy subjects and patients with *H. pylori* negative chronic gastritis (n=30) and *H. pylori* positive chronic gastritis before and after eradication therapy (n=18).

The TRVP1, CGRP expressions increased significantly in the gastric mucosa with *H. pylori* infection (in comparison with the immunodistribution of TRVP1 and CGRP obtained in the gastric mucosa with healthy subjects, and no significant changes were obtained in the distribution of SP).

In the second series of human observation, it was an unexpected result, that the distribution of TRVP1, CGRP and SP remained unchanged after the classical eradication treatment in patients, although the urea breath test showed high successful rate in bacterial eradication. The gastric mucosa did not become to be histologically negative after the eradication treatment. Interestingly the ratio between the TRVP1, CGRP positivity vs. negative remained the similar before and after eradication.

To understand the changes in histochemical distribution in the gastric mucosa, we performed acute animal experiment, when the rat gastric mucosa was exposed to endogenous (HCl) and exogenous (indomethacin) noxious agents. In these experiments presence of positive immunodistribution of TRPV1, CGRP and SP decreased acutely, that could be abolished by omeprazole (or omeprazole-like compounds) treatment (at 4 hour) (Mózsik et al., 2005b) (Figs. 7-10).

		SP positive		
		weak	medium	strong
Healthy subjects (n=20)	0%	70%	5%	25%
<i>H. pylori</i> pos gastritis (n=21)	0%	85%	5%	15%
<i>H. pylori</i> neg gastritis (n=30)	0%	70%	0	30%
<i>H. pylori</i> pos gastritis (n=18)				
Before eradication	94%	0	6%	0
After eradication	100%	0	0%	0

Table 8. Summary of result obtained in immunohistochemistry examinations for SP in gastric mucosa of healthy subjects and patients with *H. pylori* negative chronic gastritis (n=30) and *H. pylori* positive chronic gastritis before and after eradication therapy (n=18).

Fig. 7. Immunostaining for TVRP1 in rat gastric mucosa. Weak (A), medium (B) and strong (C) expression of TRVP1 by glandular cells. The weak antigen expression corresponds with immunostaining of some glands in the basal layer. In biopsies with medium expression, positive glands are found at the most in half of the mucosa, and in cases with strong TRVP1 positivity, almost all glands are stained (original magnification: 100x).

Fig. 8. Immunostaining for CGRP in rat gastric mucosa. Weak (A; only some glandular cells are positive in the mucosa), medium (B; fine granular cytoplasmic staining) and strong (C; predominantly in the basal zone, larger granular staining is observed with higher intensity) CGRP expression (original magnification: 100x).

Fig. 9. Immunostaining for SP in rat gastric mucosa. The weakly stained mucosa (A) is almost negative, however, in positive cases; some fine granular immunostaining was observed (B), corresponding to perivascular neural elements (original magnification: 100x).

Fig. 10. Schematic presentation of hypothesis for the changes in immunohistochemically demonstrated changes of TRPV1 receptor, CGRP and SP in rat gastric mucosa after application of endogenous (HCl) and exogenous (indomethacin) chemical agents without (A) and with application of omeprazole and omeprazole like compounds (B) during 4-h experimental time period.

	Histochemical expression	Number of mucosal lesions	Severity of mucosal lesions
TRVP1 <i>Omeprazole</i> (n=5-10)	↑	↓	↓
TRVP1 <i>Omeprazole like</i> (n=5-10)	↑	↓	↓
CGRP <i>Omeprazole</i> (n=5-10)	Dose dependently ↑	↓	↓
CGRP <i>Omeprazole like</i> (n=5-10)	No significant change	↓	↓
SP <i>Omeprazole</i> (n=5-10)	No significant change	↓	↓
SP <i>Omeprazole like</i> (n=5-10)	No significant change	↓	↓

↑ means increase.
↓ means decrease.

Table 9. Correlation between the drug actions and histochemistry in indomethacin-treated rats (n=5-10).

	Histochemical expression	HCl secretion
TRVP1 <i>Omeprazole</i> (n=5-10)	Dose dependent ↑	↓
<i>Omeprazole like</i> (n=5-10)	Dose dependent ↑	↓
CGRP <i>Omeprazole</i> (n=5-10)	Dose dependent ↑	↓
<i>Omeprazole like</i> (n=5-10)	Dose dependent ↑	↓
SP <i>Omeprazole like</i> (n=5-10)	No significant change	↓
<i>Omeprazole like</i> (n=5-10)	No significant change	↓

↑ means increase.
↓ means decrease.

Table 10. Correlation between the drug actions and immunohistochemistry in pylorus-ligated rats.

In this case the proton pump inhibitor acts at the level of efferent nerves. The classical eradication treatment does not link specifically to efferent or afferent nerves of the vagus.

There is no question that the 6-week time period after eradication therapy does not offer enough time for the histologically restoration of gastric mucosa in patients with chronic *H. pylori* positive gastritis.

Our explanation for the unchanged immunohistochemical distribution of TRPV1, CGP and SP of gastric *H. pylori* positive chronic gastritis before vs. after eradication treatment:

1. Six-week time period (including the time of eradication) is not enough time for the complete healing of chronic gastritis. Because of patients' complaints decreased (and the eradication treatment was mostly successful), however, the changes in gastrointestinal mucosal histology (and immunohistology) showed a lower infection, successful eradication treatment, traditional and specific immunohistological distribution of TRPV1, CGRP and SP differ from each other.
2. The six-week time period (after eradication) is probably not enough time for complete histologically recovery of chronic *H. pylori* in patients in term of histology and immunohistology.
3. The *H. pylori* bacteria as etiological factors might represent only one of the factors causing chronic gastritis (in term of histology).
4. The immunohistological distribution of TRPV1, CGRP and SP are independent on the chronic gastritis produced by different physical, chemical, bacteriological or immunological agents. It's true, that the gastric mucosa did not become histologically intact after eradication treatment. These changes in the histological picture in the gastric mucosa (before and after eradication treatment) suggest that the time period (6 weeks) was short for healing the chronic gastritis by eradication treatment. That fact is confirmed by the repeated histological examinations. Histologically healthy gastric mucosa could be studied only in 4 cases of the control biopsies. In 14 cases, the appearance of chronic gastritis became just moderated.
5. It can be suggested, that other *permanent factors* (stress, drugs) also *take also part in the development of chronic gastritis* which is in accordance with our further observations. The immunomorphology of TRPV1, CGRP and SP do not differ in chronic gastritis evoked by different factors (*H. pylori*, drugs, etc).
6. Low percentage of participants was refractory to the eradication therapy, so the persistent *H. pylori* infection before and after eradication could maintain the same immunohistochemical appearance, the same inflammatory answer.

We demonstrated that the immunodistribution of vanilloid receptor, CGRP and SP increased in patients with chronic gastritis, however, no differences were obtained in the immunohistochemical distribution of examined parameters in the gastric mucosa with *H. pylori* positive and *H. pylori* negative patients (Dömötör et al., 2006). Our presented results clearly indicate that the immunohistochemical distribution of vanilloid receptor, CGRP and SP after classical eradication treatment in patients with *H. pylori* positive chronic gastritis (by other words the capsaicin-sensitive afferent nerves) are independent from the eradication treatment.

The knowledge, that the capsaicin is able to reduce the indomethacin-induced gastric microbleeding in human healthy subjects and the involvement of TRPV1, CGRP and SP in different gastrointestinal disorders show the importance of continuation of such studies to reach a better understanding of gastric mucosal defensive mechanisms in humans (Mózsik et al., 2005a).

Similar conclusions were obtained from the results of animal experiments and human observations, when we co-applied drugs acting on efferent and afferent vagal nerve fibres (Mózsik et al., 1997, 2009) and received combined actions.

Recently, different molecular-pharmacological observations were carried out (and calculated, based on the dose-responses curves of drugs) with capsaicin, atropine, pirenzepine, cimetidine, ranitidine, famotidine, nizatidine, omeprazole, esomeprazole, PGI₂, vitamin A, β -carotene on the gastric basal acid output (BAO) in healthy human subjects (Mózsik et al., 2005), on changes of gastric transmucosal potential difference produced by ethanol (5 ml, 30 v/v% topically applied directly into the gastric mucosa by the way of endoscopic biopsy channel), on indomethacin-induced (3x25+25 mg orally) gastric microbleeding in healthy human subjects (Mózsik et al., 2007), and on gastric (basal and stimulated by betanechol, histamine and pentagastrin) acid secretion of pylorus-ligated rats (Mózsik et al., 2006) or on gastric mucosal damage produced by different chemicals (Indomethacin, HCl, ethanol, NaOH, concentrated NaCl solution) in rats (Mózsik et al., 2006).

The values of affinity (pD) and intrinsic activity (α) curves of these compounds were calculated according to standard procedures employed in molecular-pharmacology (Csáky, 1969). The values of the pD₂ (dose necessary to inhibit the gastric acid secretion and gastric mucosal damage by 50%) and pA₂ (dose necessary to produced 50% decrease in gastric acid secretion and in gastric mucosal damage) were calculated from the affinity and intrinsic activity curves. The intrinsic activity values obtained in relation to atropine ($\alpha_{\text{atropine}} = 1.00$) were taken as standard values.

The knowledge of affinity, intrinsic activity curves, values of pD₂ and pA₂ gives us an exact approach to understand the physiological and pharmacological roles of different compounds (Mózsik et al., 2006, 2007, 2009).

The following pD₂ values were obtained for the different drugs or substances inhibiting the gastric basal acid secretion (BAO): capsaicin, 5.88; atropine, 5.40; pirenzepine, 3.93; cimetidine, 2.23; ranitidine, 3.33; famotidine, 3.77; nizatidine, 3.23; omeprazole, 3.97 and esomeprazole, 3.97 (Mózsik et al., 2007). Similar results were obtained for these compounds inhibiting gastric mucosal damage produced by intragastric administration of ethanol or by orally applied indomethacin in healthy human subjects (Mózsik et al, 2005a).

The results of these observations led us to conclude that the capsaicin-sensitive afferent nerves have the most important physiological regulation of gastric basal acid secretion (BAO) and of chemicals-induced gastric mucosal damage in human healthy subjects (Mózsik et al, 2005a, 2007, 2009). Similar results obtained in animals experiments for regulation of gastric acid secretion and of gastric mucosal damage (Mózsik et al, 2006).

The unchanged functional state of capsaicin-sensitive afferentation, before and after classical eradication treatment in patients also offers to conclude an important regulatory function of gastric mucosa in patients with *H. pylori* chronic gastritis (in comparison the results obtained in patients with *H. pylori* positive gastritis vs. healthy persons) by TRVP1, CGRP and substance P during the eradication treatment.

The most important message of this work (study) is that the gastric capsaicin-sensitive afferentation has a permanent defensive role(s) in the gastric mucosal defence. Consequently the modification in the function of capsaicin-sensitive afferent nerves offer new possibilities in human medical therapy.

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This book is a comprehensive overview of invited contributions on *Helicobacter pylori* infection in gastritis and gastric carcinogenesis. The first part of the book covers topics related to the pathophysiology of gastric mucosal defense system and gastritis including the gastroprotective function of the mucus, the capsaicin-sensitive afferent nerves and the oxidative stress pathway involved in inflammation, apoptosis and autophagy in *H. pylori* related gastritis. The next chapters deal with molecular pathogenesis and treatment, which consider the role of neuroendocrine cells in gastric disease, DNA methylation in *H. pylori* infection, the role of antioxidants and phytotherapy in gastric disease. The final part presents the effects of cancer risk factors associated with *H. pylori* infection. These chapters discuss the serum pepsinogen test, K-ras mutations, cell kinetics, and *H. pylori* lipopolysaccharide, as well as the roles of several bacterial genes (*cagA*, *cagT*, *vacA* and *dupA*) as virulence factors in gastric cancer, and the gastrokine-1 protein in cancer progression.

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