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# Capsaicin-Sensitive Afferentation Represents a New Mucosal Defensive Neural Pathway System in the Gastric Mucosa in Patients with Chronic Gastritis

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<http://dx.doi.org/10.5772/52883>

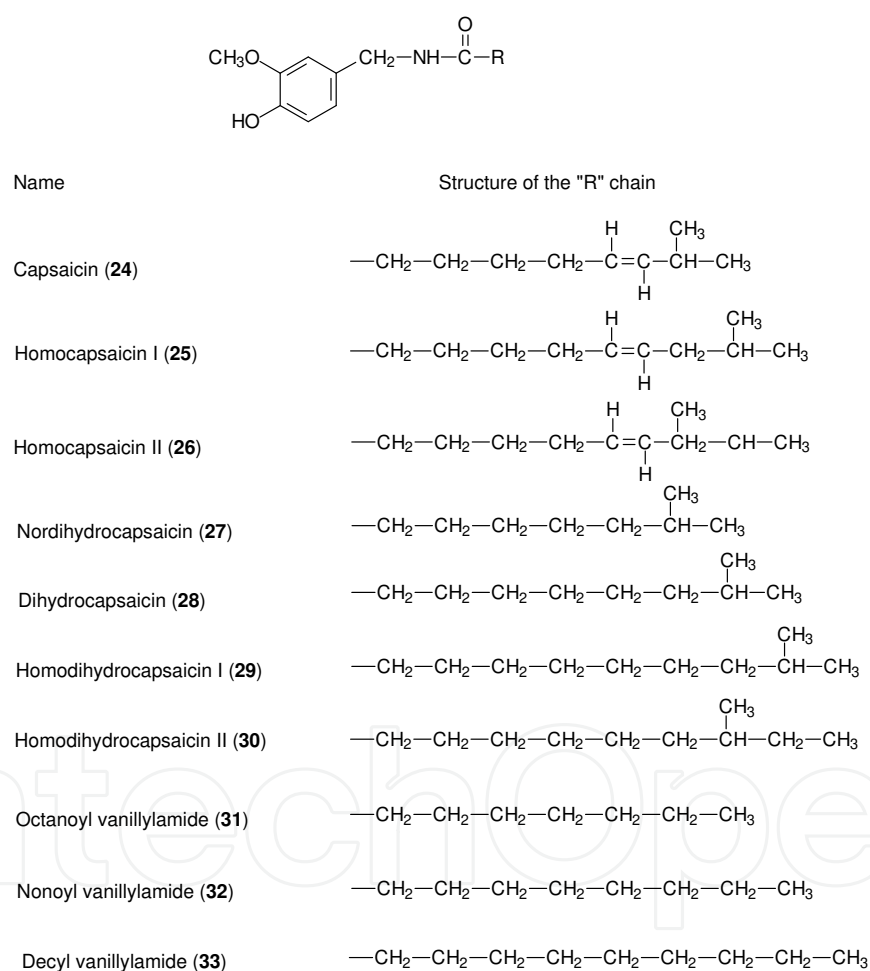
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## 1. Introduction

The name of capsaicin is generally used in the medical research, however this material does not contain a uniform chemical entity. Capsaicinoids covers 5 analogues and 2 homologues components (Mozsik et al. 2009) (Fig. 1).

It has been established that capsaicinoids interact with capsainin-sensitive afferent nerves representing a novel regulatory pathway of gastrointestinal functions (Jancsó et al. 1967, 1968, 1970). Capsaicin-sensitive afferent nerves contain a temperature-gated ion channel called capsaicin receptor or transient receptor potential vanilloid 1 (TRPV1) which is expressed by a subgroup of primary afferent nociceptive neurons (Szolcsanyi, 2004). The capsaicin receptor has been cloned (Caterina et al., 1997) and has been found to be linked to a cation channel. It is gated by capsaicin and other capsaicinoids (some vanilloids) by various treatments including low pH, noxious heat and various pain-producing endogenous and exogenous chemicals. Thus, those sensory nerve endings possessing these ion channels are susceptible to being stimulated in the gastric mucosa. Upon stimulation with capsaicin, these afferent fibers develop four response stages (excitation, sensory-blocking, long-term selective neurotoxic impairment, and irreversible cell destruction), depending on the dose and duration of exposure of the component (Mózsik et al. 2001). A low dose of capsaicin (nanograms to micrograms per kilogram) causes excitation of the nerve endings, and neuropeptides (substance P [SP], calcitonin gene-related peptide [CGRP], and somatostatin) are released (Holzer et al. 1998, 1999) (Szolcsányi 2004). These mediators can increase mucosal blood flow by vasodilatation (Holzer et al. 1991), can activate mast cells and immunocytes in

the mucosa (Stead 1992), and are involved in drug effects (Mózsik et al. 2004, 2005), 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 (Sipos et al. 2006). Notwithstanding studies supported that this gastric mucosal protective mechanism provided by capsaicin-sensitive afferent nerves exists in patients with chronic gastritis, and its extent does not depend on the presence or absence of *H. pylori* infection. In other words, the gastric mucosal protection produced by capsaicin-sensitive afferent nerves is one of the general defense mechanisms against the different noxious agents that induce chronic gastritis (Dömötör et al. 2006).



**Figure 1.** Names and chemical structures of capsaicin homologs and analogs (with knowledge and allowance of Mózsik et al. 2009).

The vagal nerve has a key-role in the development of gastrointestinal mucosal damage and prevention (Mózsik et al., 1982). The key-role of vagal nerve has been emphasized dominantly in the aggressive processes to gastrointestinal (GI) mucosa (such as in peptic ulcer disease, gastric mucosal damage, etc.) as evidenced from GI investigations in animal models

and as well as in human clinical practice. The application of capsaicin in the animal experiments was used as a specific tool to investigate those primary afferent nociceptive neurones (Szolcsányi, 2004; Buck and Burks, 1986; Holzer, 1988; 1991; Szállasi and Blumberg, 1999) involved in the different physiological, pathological processes.

Szolcsányi and Bartho (1981) were the first authors, who clearly identified the beneficial and harmful effect of capsaicin in experimental peptic ulcer in rats, following varying doses of capsaicin. Later, Holzer undertook extensive investigations on the mode of action of capsaicin on GI functions (Holzer, 1998; 1999; Buck and Burks, 1986; Szállasi and Blumberg, 1999). We also contributed during the 1980's to GI capsaicin research from studies in animal models (Mózsik et al., 1997c). Recently the new drug, lafutidine, was introduced in the medical treatment of GI mucosal damage (Ajioka et al., 2000; 2002; Onodera et al., 1995; 1999; Takeuchi, 2006). Lafutidine is a histamine histamine type 2 receptor (H2R) blocking compound which uniquely has typical capsaicin actions on the target organ.

Capsaicin-sensitive vagal neural afferentation is one of the defensive mechanisms. These nerves have been shown to play a role in gastric mucosal protection by preventing drug-induced mucosal injury in animals (Abdel-Salam et al. 1999; Mózsik et al. 1997a; Reinshagen et al. 1996) and by decreasing the amount of indomethacin (IND)-induced gastric micro-bleeding in healthy human subjects (Kang JY et al. 1995; Mózsik et al. 2004b; Mózsik et al. 2005). These mechanisms are well known to be important in protection against gastritis caused by various harmful effects. The TRVP 1 receptors were also detected in the area postrema and in the nucleus tractus solitarius, where the afferent fibres of the vagus nerve taper, and have key role in regulation of gastric functions i.e. secretion, motility and protection mechanisms.

The vagus nerve consists of 10% efferent nerves, 90% afferents. About 10% of these afferent nerves are capsaicin-sensitive. The amount of efferent nerves and the capsaicin-sensitive afferent nerves is roughly equal in the vagus nerve. Capsaicin exposure exerts various responses in these afferent nerves depending on dose and exposure duration (excitation, sensory-blocking, long-term selective neurotoxic impairment and irreversible cell destruction) (Vincze et al. 2004). During exposure to 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, are released from the nerve endings (Caterina et al. 1997; Mózsik et al. 2001; Holzer 1998). These mediators are responsible for increasing mucosal blood flow by vasodilatation (Holzer 1999), activation of mast cells and other immune cells in the mucosa (Szolcsányi 2004; Holzer et al. 1991) and defense of gastrointestinal mucosa.

Capsaicin has been used in human studies, looks to be a suitable treatment tool in several fields of medicine that can be seen from several running and completed multicentric controlled studies worldwide. The United States Pharmacopeia (USP) describes the list of capsaicins and their definition, identification, melting range, and content of capsaicin, dihydrocapsaicin and other capsaicinoids as follows (USP30-NF25. 2006 Edition, pp.1609): capsaicin contains not less than 90.0 % and more than 110.0 % of the labelled percentage of total capsaicinoids. The content of capsaicin is not less than 55 %, and the sum of the contents of capsaicin and dihydrocapsaicin should not be less than 75 %. The content of other

capsaicinoids should not be more than 15 %, all calculated on the dried basis. The circumstances of plant cultivation, preparation, storage and other facts are summarized in the drug master file (DMF). The DMF of capsaicin originated from India was signed by Food and Drug Administration (FDA) in the United States as existing registration, which allows the usage of capsaicin as basic source for capsaicin-containing drugs. This type of capsaicinoids (briefly capsaicin) was used in our previous studies (Mozsik et al. 2009a, 2009b, 2011).

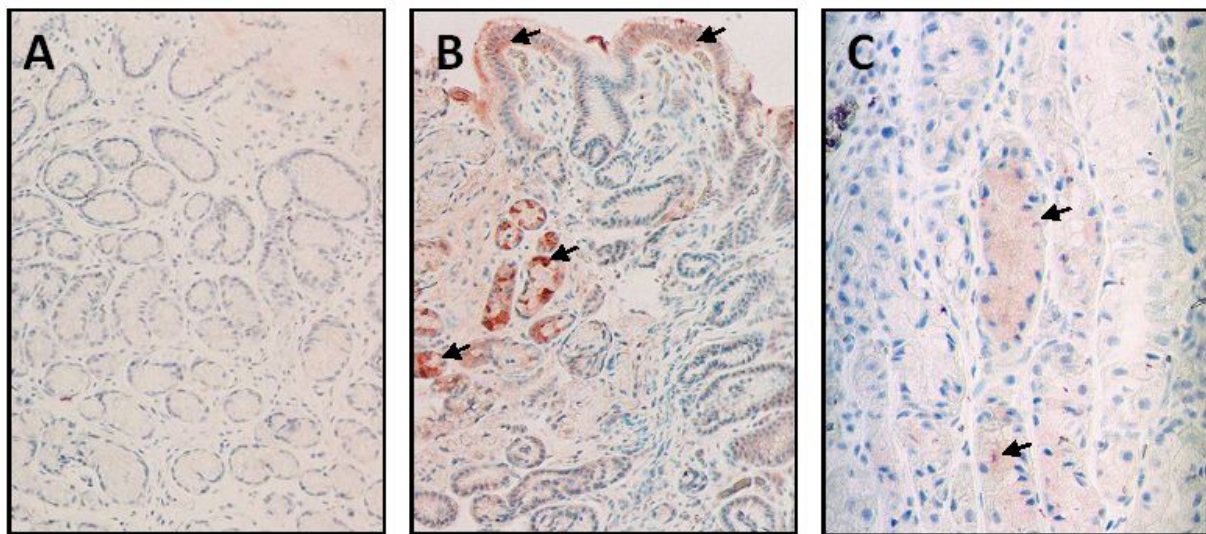
Gastritis is a pathomorphological appearance of inflammation in the gastric mucosa. Acute and chronic gastritis can be differentiated on the basis of the development and process of the disease. Chronic gastritis may be caused by different factors such as *Helicobacter pylori* infection, bacterial overgrowth in a hypochlorhydric stomach, autoimmune mechanisms, or chemical agents such as long-term nonsteroidal anti-inflammatory drug (NSAID) treatment, and bile reflux (Owen 2003; Appelman 1994, Szabo et al. 2012), for details about mechanisms we refer to the other chapters of this book. Nowadays, the importance of *Helicobacter pylori* infection is increasing as the main causative factor in gastric diseases in humans. This bacterium is highly prevalent in many countries (Parsonnet 1995) and it increases the risk for development of gastric and duodenal ulcer disease, gastric cancer, and gastric mucosa-associated lymphoid tissue lymphoma (Janulaityte-Gunther et al. 2005; Mitani et al. 2004; Peng et al. 1998; Salih et al. 2005; Zhang et al. 2005a, 2005b). Dysfunction of gastrointestinal mucosal defense mechanisms is also involved in the development of gastric diseases. Capsaicin-sensitive afferent nerves take part in gastric mucosal protection in animals (Mózsik et al. 1997a; Reinshagen et al 1996) and in healthy human subjects (Kang et al. 1995; Mózsik et al. 2004a, 2005a), and the presence of these fibers is proved to play a role in the development of human gastrointestinal disorders including gastritis, peptic ulcer, polyp without and with dysplasia, tumor, and inflammatory bowel diseases (Dömötör et al. 2005; Vincze et al. 2004). 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 (Sipos et al. 2006).

## 2. Recent results in human studies

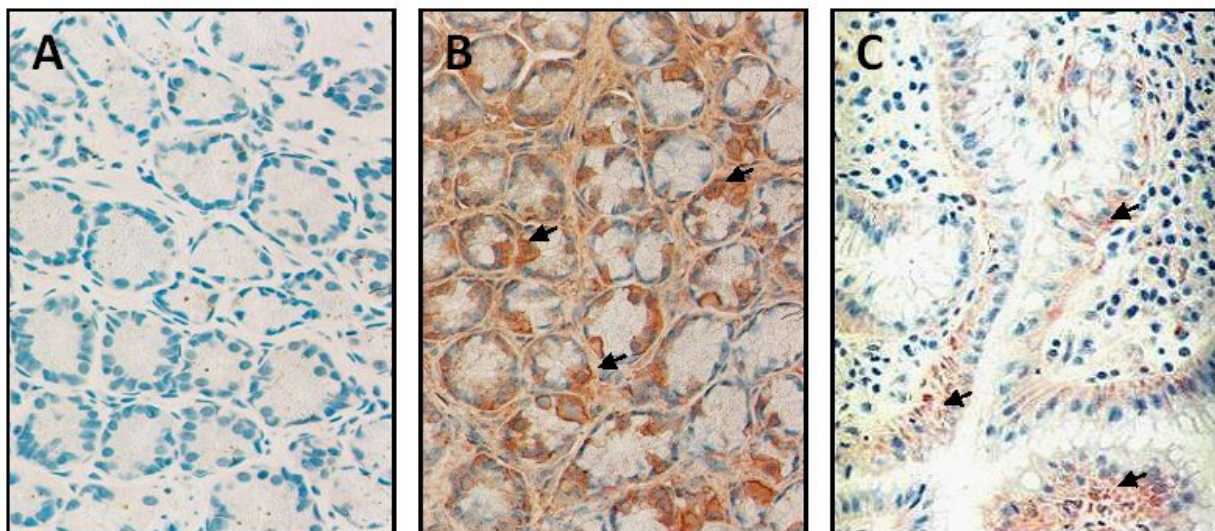
Presentation of capsaicin-sensitive afferentation in the *H. pylori* positive and *H. pylori* negative chronic gastritis in patients has been studied by Mózsik et al. (2011): The symptoms of patients suffering from chronic gastritis with or without *H. pylori* infection (*H. pylori* positive, n=21, age 39-68 years, screened with [<sup>14</sup>C] urea breath test, rapid urease test, Warthin-Starry silver staining and specific histological examinations; *H. pylori* negative, n=30, age 39-68 years) were nonspecific including gastric discomfort sensation, nausea, loss of appetite and vomiting. The gastric tissue samples from the stomach and antrum were examined by an independent histopathologist and classified of chronic gastritis according to the Sydney's System (Price et al. 1991). The immunohistological studies were carried out on formalin fixed, paraffin embedded tissue samples of gastric mucosa using the peroxidase-labeled polymer method (Lab Vision Co., Fremont, USA). SP was detected by the NC1/34HL rat mono-



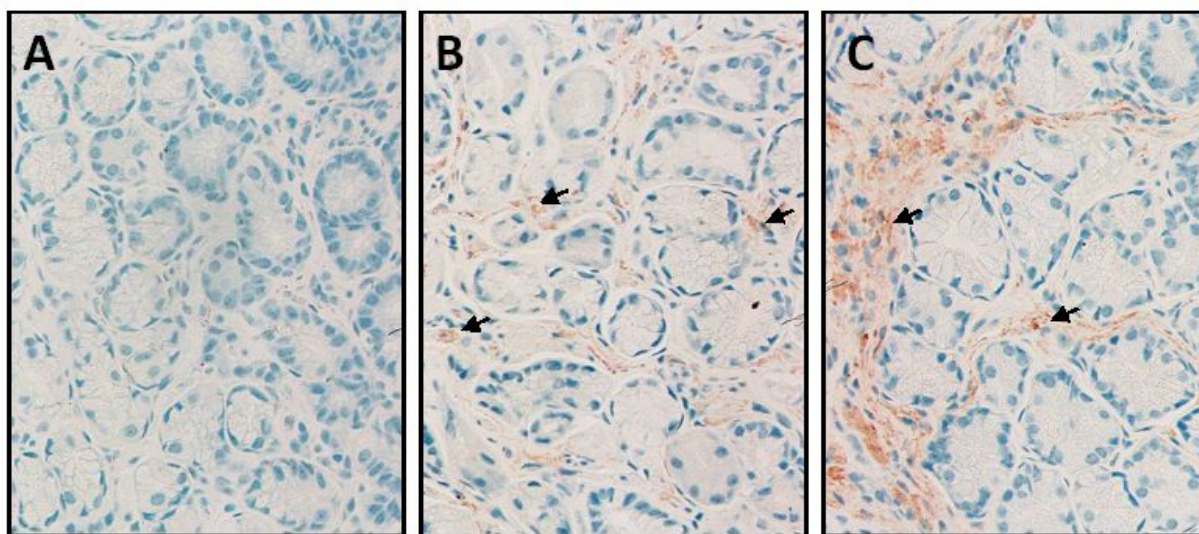
clonal antibody, the TRPV1 receptor and CGRP were labeled using polyclonal rabbit antisera (all from Alcam Ltd., UK, Cambridge) (Dömötör et al. 2006) (Figs. 2-4).



**Figure 2.** Immunohistochemical distribution of capsaicin receptor (transitoric receptor potential vanilloid) (TRPV1) in the gastric mucosa of a healthy (A) and of patient with *H. pylori* negative (B) and *H. pylori* positive (C) chronic gastritis. Arrows indicate the immunosigns in the epithelial layer of the gastric mucosa (original magnification: 100x). From the ref. (Mózsik et al. 2011), with permission.



**Figure 3.** Immunohistochemical distribution of calcitonin gene-related peptide (CGRP) in the gastric mucosa of healthy subject (A), of patient with *H. pylori* negative (B) and *H. pylori* positive (C) chronic gastritis. Arrows demonstrate the immunosign in the epithelial layer of the gastric mucosa (original magnification: 100x). From the ref. (Mózsik et al. 2011), with permission.



**Figure 4.** Immunohistochemical distribution of substance P (SP) in gastric mucosa of healthy subject (A), of patients with *H. pylori* negative (B) and positive (C) chronic gastritis. Arrows show the immunosigns in the epithelial layer of the gastric mucosa (original magnification: 100x). From the Ref. (Mózsik et al 2011), with permission.

Presentation of capsaicin-sensitive afferentation of vagal nerve in patients with *H. pylori* positive chronic gastritis of patients, before and after eradication treatment (Mózsik et al 2011): Very recently the same clinical and immunohistochemical examinations were carried out as those mentioned above in patients with *H. pylori* positive chronic gastritis before and after eradication treatment. These observations were carried out in 38 persons, including 20 healthy subjects and 18 patients with *H. pylori* positive gastritis. The age of persons with histologically intact gastric mucosa (controls) were between 41 and 67 years (mean=52.2 years). The age of patients (6 males, 12 females) was 39 to 68 years (mean = 56.4 years).

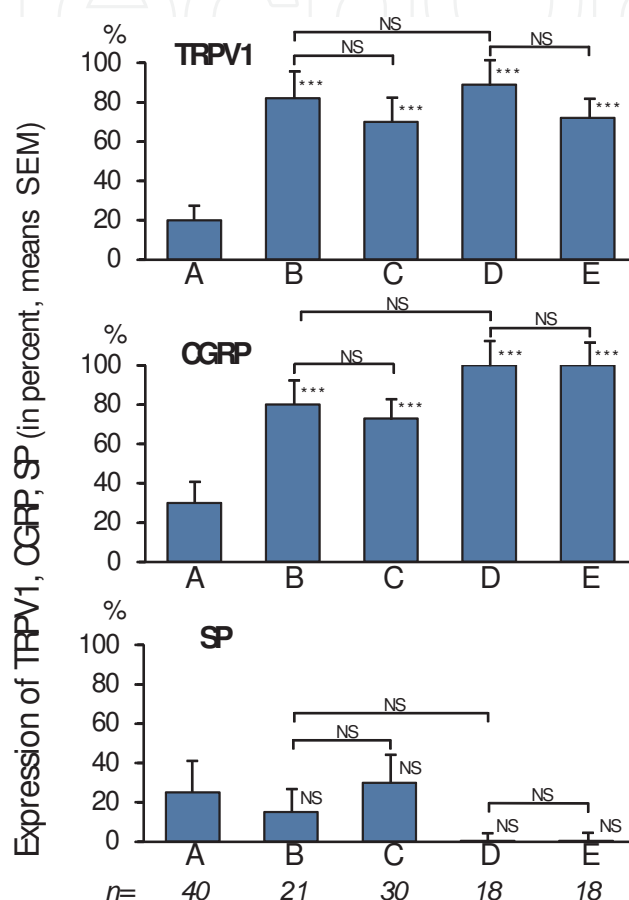
The time period between the first and control gastroscopy was 6 weeks. The biopsies were taken from the corpus and antrum of patients with chronic gastritis, before and after eradication treatment, and from healthy persons. *H. pylori* positive patients underwent 7 days eradication treatment with combination of double dose PPI (pantoprazole 2x40 mg/day), amoxicillin (1000 mg twice daily) and clarithromycin (500 mg twice daily) according to current European guidelines (Malferteiner et al. 2007). After this one week combination treatment, patients continued to take normal dose of PPI for another week. The *H. pylori* infection was detected before and after by [ $^{14}$  C] urea breath test, rapid urease test, Warthing-Starry silver staining and specific histological and immunohistological examinations. The results of eradication treatment was successful in 89%, the gastric histology indicated normal picture in 22% of cases, and in 78 per cent patient the mucosa showed moderate gastritis (Lakner et al. 2011).

Expression of TRPV1 receptor, CGRP and SP in the gastric mucosa of patients with *H. pylori* negative and positive chronic gastritis, and before and after successful eradication treatment (Mózsik et al 2011): The expression of TRPV1 and CGRP increased in the gastric mucosa of patients with chronic gastritis, however, it was an unexpected that the increase expression of



TRPV1 and CGRP did not depend on the presence of *H. pylori* infection. The changes in expression of SP were not significant between these groups of patients.

Another surprising result was obtained in patients with *H. pylori* positive chronic gastritis before and after successful eradication treatment. The extent of expression of TRPV1, CGRP remained at the same level after eradication. No significant changes were obtained in the expression of SP in the gastric mucosa in these patients (Fig. 4) (Mózsik et al 2011).



**Figure 5.** Changes in the expression of capsaicin receptor (TRPV1), calcitonin gene-related peptide (CGRP) and substance P (SP) in the human gastric mucosa of healthy volunteers (histologically intact) (A), *H. pylori* positive (B), *H. pylori* negative (C) and *H. pylori* positive before (D) and after eradication (pantoprazole 40, amoxicillin 1000 and clarithromycin 500 mg, all two times per day, for seven days) (n=number of patients) (Mózsik et al 2012).

These findings suggest potential role of capsaicin-sensitive afferent vagal nerve in the development of chronic gastritis and the eradication treatment (Mózsik et al 2011): From the experimental observations it could be concluded that actions of capsaicin are dose-dependent (Mózsik et al. 2001, 2005a, 2009b). The types of gastric mucosal injuries could be prevented by application of small doses (200 to 800 µg/person) of capsaicin (Mózsik et al. 2001). Results of these observations suggest mucosal protecting effect of capsaicin (acting via the stimulation of capsaicin-sensitive afferent fibres of vagal nerve) in healthy human subjects. These observations showed that the expression of TRPV1 and CGRP increased significantly in infla-



mated chronic gastritis, and no significant change was obtained in SP levels. However, these immunohistochemical results did not differ in patients with *H. pylori* positive and negative chronic gastritis. Capsaicin-sensitive afferentation did not differ before and after (6 weeks) successful eradication treatment in patients with chronic *H. pylori* positive gastritis (meanwhile the control biopsy was normal in 22% and in 78% indicated in moderated histological picture of gastritis) (Lakner et al. 2011).

Explanation of study group of the for the unchanged immunohistochemical distribution of TRPV1, CGRP and SP of gastric *H. pylori* positive chronic gastritis before vs. after eradication treatment were as follows (Mozsik et al. 2011):

1. Six week time period (including the eradication treatment) is not enough time for the complete healing of chronic gastritis.
2. The six-week time period (after eradication treatment) is probably not enough time for complete histologically recovery of chronic *H. pylori* positive infection 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 (expression rate) of TRPV1, CGRP and SP are independent on the chronic gastritis produced by different physical, chemical, bacteriological or immunological agents. However, the increased expression of TRPV1, CGRP is involved in the gastric mucosal damage and the normalization of these changes can be obtained by other way as the classical eradication treatment (Lakner et al. 2011).

Kozłowski et al. (2011) concluded from their study on chronic gastritis: 1. Chronic superficial gastritis coexists with significantly higher proliferative activity of gastric mucosal glandular epithelium, particularly in relation to the prepyloric area and 2. Changes of proliferative activity of gastric mucosal glandular epithelium are independent of age, histotopography and of *H. pylori* colonization.

Recent investigations showed that the expression of TRPV1 and CGRP increased significantly in the epithelial layer of the gastric mucosa in patients with *H. pylori* - positive and -negative chronic gastritis. The significant etiological role of *H. pylori* in the development of chronic gastritis has received great attention in the pertinent literature; for this reason, we compared the differences in TRPV1, CGRP, and SP expression in *H. pylori* positive or -negative chronic gastritis, suggesting their etiological role in the development of chronic gastritis. No significant differences were obtained between *H. pylori*-positive and *H. pylori*-negative patients, but values of both groups with chronic gastritis differed significantly from those of histological intact mucosa of healthy human subjects. Results also indicated that chronic gastric inflammation is one of the general tissue reactions to different noxious agents, and *H. pylori* is only one of these in patients. It must be emphasized that clinicians are able to specifically demonstrate the presence of *H. pylori* (by UBT, rapid urease test, and specific histological staining), however, we have no specific methods for well demonstration of other (suggested) etiological factors.

In animal experiments, different noxious agents produce the same (or basically similar) pathological, biochemical (oxygen free radicals), etc., events in the development of gastrointestinal mucosal injury and its prevention (Mózsik et al. 1992). Gastric mucosal damage can be produced by direct application of ethanol and indomethacin and it can be dose dependently prevented by the topical application of capsaicin in healthy volunteers (Mózsik et al., 2005a). Endogenous (increased production of gastric HCl in 4-hr pylorus-ligated rats) and exogenous (indomethacin given s.c. in a 4-hr experiment, without pylorus ligation) factors produced changes in functional status and damaged the gastric mucosa in rats. The immunohistochemical distribution of TRPV1, CGRP, and SP decreased significantly during this time; the levels of TRPV1 and CGRP returned to those of healthy controls dose dependently by application of omeprazole and omeprazole-like compounds, and no significant change was detected in the immunodistribution of SP (Mózsik et al. 1997b). There is no real explanation for the different expression rates of TRPV1 and mediators released from the sensory nerves. Similar differences in TRPV1, CGRP, and SP have been observed in many other conditions (in acute animal models and in patients with chronic gastrointestinal disorders). The following explanations have been suggested for these differences in expression of TRPV1 and mediators released from sensory nerves (Dömötör et al., 2007): (1) the regulation of SP differs from that of TRPV1 and CGRP regarding the development of chronic gastritis and (2) the sensitivity of SP regulation is lower than in the cases of TRPV1 and CGRP. The increased level of TRPV1 and CGRP is accepted as a signal of an increased defense mechanism produced by capsaicin-sensitive afferent nerves in animal experiments (Mózsik et al. 2005a), and the topical application of capsaicin dose-dependently prevented the mucosal injury produced by intragastrically applied ethanol and indomethacin in healthy human subjects (Mózsik et al. 2005b). These findings suggest that increased expression of TRPV1 and CGRP is associated with increased gastric mucosal protection. This gastric mucosal protective mechanism provided by capsaicin-sensitive afferent nerves exists in patients with chronic gastritis, and its extent does not depend on the presence or absence of *H. pylori* infection. In other words, the gastric mucosal protection produced by capsaicin-sensitive afferent nerves is one of the general defensive mechanisms against the different noxious agents that induce chronic gastritis.

### 3. Conclusions

The results of above mentioned animal and human observations indicated clearly the following considerations:

1. Both acute and chronic gastritis can be induced by different reasons, like chemicals (drugs) or bacteria (most emphasized one *H. Pylori*). Both *H. pylori* positive and negative gastritis can be acute or chronic. In case of patients with *H. pylori* negative gastritis, the therapeutic approach follows the traditional medical treatment, while *H. pylori* positive patients with gastritis are suggested a rational eradication treatment only (accepted by many international consensus meetings).

Mózsik et al. and Lakner et al. (2011) have demonstrated that while chronic *H. pylori* positive gastritis heals entirely after a successful eradication therapy (which represents an important step to prevent development of gastric cancer), the extents of TRVP1, CGRP remained in increased level (in comparison to the normal gastric mucosa). This indicates that there is at least one other important defensive mechanism than antibiotic eradication treatment, the capsaicin-sensitive afferentation of vagal nerve (results clearly indicated that independent from *H. pylori* status and independent from eradication).

Generally it can be concluded that: 1. there can be different mucosal defensive mechanisms playing key role in treatment of *H. pylori* positive chronic gastritis: a. eradication treatment and b. stimulation of capsaicin sensitive afferentation; 2. eradication treatment is independent from capsaicin-sensitive afferentation (defensive) mechanism; 3. it should be considered to amend treatment protocols of *H. pylori* positive chronic gastritis (conventional eradication therapy and success control) with modification of functional state of capsaicin-sensitive afferentation. Medical effect of capsaicin for modification of capsaicin-sensitive afferent nerves depends on its dosages, more clinical findings are needed in the field, that observations are in progress (Mózsik et al. 2009b, 2011).

## Acknowledgements

This chapter was supported by MEDICZIM Kft, Hungary and ALAPITVANY AZ EGESZSEG UGYEBEN DOLGOZOKERT, Hungary.

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