Chapter 10

Capsaicin-Sensitive Afferent Nerves and the Human Gastrointestinal Tract

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1. Introduction

Capsaicin is an active ingredient of red pepper and paprika. These plants are well known and used in every day of the culinary practice for about 9000-9500 years.

It was an important discovery that the capsaicin (capsaicin, dihydrocapsaicin, nordihydrocapsaicin and other capsaicinoids) specifically modify the function of certain nerves, later named to capsaicin sensitive afferent nerves (Jancsó et al., 1967; 1968; 1970).

Capsaicin activates the capsaicin (vanilloid) receptor expressed a subgroup of primary afferent nociceptive neurons (Szolcsányi, 2004). The capsaicin receptor has been cloned (Caterina et al., 1997) and turned out to be a cation channel. It is gated besides capsaicin and other capsaicinoids (some vanilloids) by low pH, noxious heat and various pains – producing endogenous and exogenous chemicals. Thus, these sensory nerve endings equipped with these ion channels are prone to be stimulated in gastric mucosa.

The action of capsaicin on the capsaicin sensitive afferent nerves is dose dependent (Szolcsányi and Barthó, 1981; Szolcsányi, 1984; 1997; 2004; Abdel-Salam et al., 1999; 2001; Mózsik et al., 2001). Szolcsányi indicated four different stages of capsaicin action (depending on the dose and duration of the exposure of the compound): a. excitation (stage 1); b. sensory blocking effect (stage 2); c. long-term selective neurotoxin impairment (stage 3) and d. irreversible cell destruction (stage 4) (Szolcsányi, 1984). The stages 1 and 2 are reversible; meanwhile the stages 3 and 4 are irreversible compound-induced actions on the capsaicin sensitive afferent nerve. These stages of capsaicin actions can be detected in the gastrointestinal (GI) tract (Mózsik et al., 2001) in animal experiments.

The vagal nerve has a key-role in the development of GI mucosal damage and prevention (Mózsik et al., 1982). The potency of vagal nerve has been emphasized dominantly in the aggressive processes to GI mucosa (such as peptic ulcer disease, gastric mucosal damage, etc.) in both animal models and in human investigations. The „chemical" and „surgical" vagotomy widely used in the treatment of patients with peptic ulcer disease in the years up to middle of 1970 (Karádi and Mózsik, 2000). By the other words, the primary aims of this therapy were to decrease the activity of vagal nerve at the level of efferent nerves in the target organs.

The application of capsaicin in the animal experiments was used as a specific tool to approach the group of primary afferent nociceptive neurons (Szolcsányi, 2004; Buck and Burks, 1986; Holzer, 1988; 1991; Szállasi and Blumberg, 1999, Holzer, 2013) involved in the different physiological, pathological processes and medical therapy in human healthy subjects and in patients with different GI disorders as well those treated with nonsteroidal anti-inflammatory drugs (NSAIDs).

Szolcsányi and Barthó (1981) were the firsts, who clearly indicated the beneficial and harmful effect of capsaicin in the peptic ulcer disease in rats on dependence of applied doses of capsaicin. Later, Holzer started with a very extensive research work with capsaicin in the field of gastroenterology (Holzer, 1998; 1999; Buck and Burks, 1986; Szállasi and Blumberg, 1999, Holzer, 2013). Our group also participated in the GI capsaicin research in animals experiments from 1980 (Mózsik et al., 1997) (the historical background see the chapter written by Szolcsányi, 2014).

Even new drug, Lafutidine, was developed in the medical treatment of GI mucosal damage (Ajioka et al., 2000; 2002; Onodera et al., 1995; 1999; Takeuchi, 2006). The Lafutidine is a histamin-2-receptor (H_2R) blocking compound showed typical capsaicin actions at the target organ.

The new and interesting results obtained with capsaicin application in animal experiments offered excellent tools to approach the different events of human GI physiology, pathology and pharmacology and to produce new drug or new drug combinations in human healthy subjects and patients with different GI and other diseases (myocardial infarction, thrombophylia, rheumatoid arthritis, chronic pain killer use).

We started clinical studies with capsaicin from 1997 (Mózsik et al., 1999; Debreceni et al., 1999; Mózsik et al., 2004a; 2004b; 2005) and these studies incorporated the different regulatory mechanisms of capsaicin in the human stomach, gastric mucosal preventive effects of capsaicin(noids) on the NSAID-induced gastric mucosal damage, chronic gastritis with Helicobacter pylori (H. pylori) positive and negative gastritis (with and without eradication treatment). We performed immuno-histochemical examinations of capsaicin receptor (TRPV1), calcitonin-gene-related peptide (CGRP), substance P (SP) in the human GI mucosa of patients with various GI disorders, took significant steps in the development of capsaicin containing drug and drug combinations (with aspirin, diclofenac, Naproxen), including the preparation of protocols for human phase I. examinations [and to carried out these examinations after the receiving permission from the National Institute of Pharmacy (Budapest, Hungary) and National Clinical Pharmacological and Ethical Committee of Hungary].

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These studies were carried out as propective, randomized and multiclinical studies of human healthy subjects and in patients with various gastrointestinal disorders including gastric mucosal damage produced by application of NSAIDs or H. pylori infection.

The aims of this review are: (1) to give a short summary on the actions of capsaicin on the human gastrointestinal tract (dominantly on the stomach), (2) to indicate some details of gastroprotective actions of capsaicin in human healthy subjects; (3) to demonstrate the capsaicin-induced gastric protective effects against the NSAID-(selective and non-selective COX inhibitor) induced gastric microbleedings in human healthy subjects; (4) to prove the independency of TRPV1 and CGRP expression from the presence of the H. pylori positive or negative chronic gastritis, the efficacy of successfully carried out eradication treatment in patients with H. pylori positive gastritis in patients; 5. to indicate the clinical pharmacological problems of plant origin capsaicin in humans (in term of drug processing); (6). to point out that the gastroprotective effects of capsaicin (given orally in stimulatory doses of capsaicin on the capsaicin-sensitive afferent nerves) to human healthy subjects, and as treatment to patients who are under chronic NSAID use (like patients with myocardial infarction, stroke, thrombophylia, rheumatic diseases, etc.).

In terms of classical pharmacology we would like to demonstrate clearly in the human observations that the applied doses of capsaicin stimulate the capsaicin-sensitive afferent nerve with a clear cut exclusion of the existence of capsaicin desensitation.

On the other hand, our research activity clearly demonstrates the different difficulties of capsaicin(oids) application as new gastroprotective drug for healthy subjects and for patients with different GI disorders and NSAIDs use in regards to toxicology plant cultivation, storage, chemical detection and standardization questions as well as permission requests from authorities needed prior the launch of industrial processing of plant-derived, orally applicable drug or drug combinations.

2. Materials and methods

The observations were carried out in 198 healthy human subjects aged 25-65 years (40± 10 years) and in 178 patients with various GI disorders (gastritis, erosion, ulcer, polyps, cancer and chronic inflammatory bowel diseases, polyps, precancerous states, colorectal cancer), aged ranged 25-75 years (45±10), 69 patients with chronic gastritis 39-68 years (mean: 56.4 years) (altogether 445 healthy persons and GI patients).

The observations were carried out at First Department of Medicine, Department of Pharmacology and Pharmacotherapy and Institute of Pharmaceutical Chemistry, University of Pécs, Hungary, in the Department of Gastroenterology of Petz Aladár Teaching Hospital, Győr, Hungary, in the Department of Gastroenterology of Markusovszky Hospital, Szombathely, Hungary (and their relevant Departments of Pathology), in Histopatology Ltd., Pécs, Hungary and at our industrial research partner (PannonPharma Ltd., Pécsvárad, Hungary).

The human healthy subjects and patients were included into the groups of different randomized, prospective studies (see later).

The classical human clinical pharmacological phase I examinations were carried out in 15 healthy males in each protocol (additionally up today, 30 human healthy subjects for human phase I examinations for aspirin plus capsaicin and diclofenac plus capsaicin) (some parts of these observations are presented by the book chapter written Mózsik et al., 2014).

The physical, laboratory, and iconographic examinations were normal in the healthy human subjects, in patients with various GI disorders.

The healthy persons were randomized into different groups of prospective, randomized and prospective studies for evaluation the effects of capsaicin on:

1. gastric basal acid secretion (BAO) (Mózsik et al., 1999, 2005);
2. changes in cations, anions, albumin concentration (and outputs) of gastric secretory responses (Mózsik et al., 2004a; 2005);
3. gastric emptying (Debreceni et al., 1999);
4. sugar (glucose) loading test (75 g given orally) (Dömötör et al., 2006b);
5. gastric transmucosal potential difference (GTPD) alone (Mózsik et al., 2005);
6. GTPD measurement after intragastric administration of ethanol and capsaicin application (Mózsik et al., 2005);
7. indomethacin-induced gastric microbleedings without and with capsaicin (Fisher and Hunt, 1976).

The different doses of capsaicin (1 – 8 μg/100 mL in saline solution) were intragastrically given to identify the ED_{50} values on the gastric basal acid secretion. These doses of capsaicin were used to determine direct action of capsaicin on the gastric transmucosal potential difference (GTPD) (without and with intragastric administration of ethanol) and indomethacin-induced gastric microbleedings.

The all of the healthy volunteers received capsaicin in doses with random allocation. In the observations to study the gastric emptying, sugar loading test, the effect of the ED_{50} value (400 μg intragastrically given) of capsaicin was tested.

The 178 patients with different GI disorders were studied by immunohistochemical examinations of biopsy samples. The histological diagnosis was established on the opinion of independent pathologist. The immunohistochemical examinations for capsaicin receptor, CGRP, SP were carried out on the same on paraffin-embedded tissues samples from which the classical histological diagnosis was established by the independent pathologist (Dömötör et al., 2005, 2006).

The patients with chronic gastritis (69 patients) were divided H. pylori positive and negative groups. Smaller group of patients with H. pylori infection were studied further after classical eradication treatment had been performed.

The observations were carried out according to the method of Good Clinical Practice (GCP). The studies were carried out from 1997 up to now, which were permitted by the Regional

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Ethical Committee of University of Pécs, Hungary. Written informed consent was obtained from all participants.

The following main methods were used in the human observations:

2.1. Determination of gastric basal acid out (BAO)

Determination of gastric basal acid out (BAO) in human healthy subjects: After an overnight fasting, a nasogastric tube was introduced at 8.00 a.m., and the total gastric content was suctioned. Than the newly secreted gastric juice was suctioned every 15 min for 1 h (BAO). The healthy subjects received intragastrically capsaicin (100, 200, 400 and 800 μg ig.), atropine (0.1-1.0 mg sc.), Pirenzepine 25-50 mg, famotidine (20-40 mg orally), ranitidine (150-300 mg orally), cimetidine (100-1000 mg orally), Omeprazole (20 – 40 mg iv.) and Esomeprazole (20-40 mg orally) given for determinations their dose responses curves (Mózsik et al., 2005; 2007; Szabó et al., 2013).

Gastric acid secretion was measured by titration of gastric juice with 0.1 N NaOH to pH 7.0 (pH titrimeter, Radelkis, Budapest). The gastric acid outputs were expressed as mmol/h (means ± SEM).

2.2. Determination of affinity and intrinsic activity curves

Determination of affinity and intrinsic activity curves for drugs inhibiting BAO in healthy human subjects: The applied doses of drugs were expressed in molar values, which were used to determine the affinity and intrinsic activity curves of the different drugs by the method of Csáky (1969). For drawing the affinity and intrinsic activity curves the doses of various drugs were expressed in [-] molar values, which offered to analyze the drug actions on the BAO according to the classical molecular pharmacological methods. We identified the pD_2 values (necessary doses of drugs to produce 50 per cent inhibition on BAO values). The effect of atropine ($\alpha_{atropine}$=1.00) in case of identification of intrinsic activity curves for other drugs and capsaicin (Mózsik, 2006).

2.3. Chemical composition of gastric juice without and with capsaicin application

These observations were carried out in the same healthy human subjects. The concentrations of Na^+, $K^+$and calcium^{2+}in the gastric juice were measured flamephotometrically. The concentration of $Mg^{2+}$was measured by atomic absorption spectrophotometrically, the chloride concentration by colorimetric method, the protein content by the method of biuret reaction. The 400 μg of capsaicin (as ED_{50} value) was used in these studies.

2.4. Calculation of „parietal" and „ non-parietal" components of gastric secretory responses without and with capsaicin

The chloride linked to $H^+$and sodium was calculated for the determination of „parietal" (chloride linked to H^+) and „non-parietal" (linked to sodium) components of gastric BAO (Hollander, 1934).

2.5. Measurement of gastric transmucosal potential difference (GTPD)

GTPD was measured during endoscopy. The exploring mucosal electrode was passed through the biopsy channel of gastroscope and the reference electrode was placed on the volar surface of the left forearm. The electrodes were connected to a digital voltmeter (Radelkis, Budapest, Hungary, OP 211/1). GTPD measurements were done at the greater curvature of the gastric body and the results were expressed in –mV (without and with intragastrically administration of different doses of capsaicin) (Hossennbocus et al., 1975; Mózsik et al., 2005). Five mL capsaicin (300 mL/L, diluted in saline) was intragastrically applied and only saline solution was given to identify the baseline in GTPD. The ΔGTPD values were expressed in –mV, ΔGTPD max was calculated at five minutes after intragastric application of capsaicin.

2.6. Effect of capsaicin on ethanol-induced changes GTPD changes

The GTPD baseline was identified. Then ethanol (5 mL, 300 mL/L) was intragastrically given. The GTPD change was determined after the ethanol had been passed through the biopsy channel of gastroscope without and with capsaicin administration (given in different doses in the same pathway after 1 min of ethanol administration).

2.7. Measurements of gastric microbleeding produced by acute application of indomethacin (without and with capsaicin administration) in healthy human subjects

Non-selective COX inhibitor, indomethacin (IND) was used to induce gastric microbleeding. The extents of IND-induced gastric microbleeding were measured in healthy human subjects by the method of hemoglobin concentration in the gastric juice respecting the value of gastric emptying rate (Fisher and Hunt, 1976). The details of this method were described in one previous paper (Mózsik et al., 2005).

2.7.1. Baseline of gastric mucosal microbleedings in acute observations with human healthy subjects

The baseline of gastric microbleeding was measured in the gastric juice without application of any drug and/or capsaicin. The hemoglobin concentration was determined. The extent of gastric emptying was measured with application of phenol red into the stomach (by the method of Fisher and Hunt 1976; Nagy et al., 1984). The extent of gastric microbleeding was expressed in mL/day (means ±SEM), and this value was taken as baseline (used as control for other observations).

2.7.2. Capsaicin-induced acute mucosal protection on the IND-induced acute gastric microbleeding in healthy human subjects

The healthy human subjects received IND (3x25 mg given orally for a day), and the forthcoming day the gastric microbleeding was measured on forthcoming day, when these healthy human subjects also received 25 mg IND orally. The extent of gastric microbleeding was measured as mentioned above, and its value was expressed as mL/ day (means ± SEM).

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2.8. Measurements of gastric emptying

The gastric emptying measurements were performed on two consecutive days by the same protocol, without capsaicin on first day and with capsaicin (400 μg orally given, ED_{50} value) on second day. The measurement procedure was the following. The healthy human subjects went on an overnight starvation and the observations were started at 8.00 a.m. In total, 100 mL of ^{13}C-octanoid acid (Izinta, Budapest, Hungary) was given for the gastric emptying measurements. This material was given in 200 mL physiological saline and 75 g glucose was added to the solution. The volunteers exhaled into a plastic bag with a volume of 0.5 L. The first air sample was considered as reference. Then, the volunteers swallowed the test solution and gave air samples in every 15 min. The IRIS performed the infrared spectroscopy (IRIS, Izinta, Budapest, Hungary) measurements and calculated the delta over base (DOB) values. This value was directly proportional to the ratio $^{13}CO_2$ and $^{12}CO_2$ (DOB is about $^{13}CO_2/^{12}CO_2$) in the air sample. When we respected the DOB values against to the time in the graph, we obtained a gastric emptying curve. On this curve, we could consider the following four parameters to characterize gastric emptying rate: 1. maximal value of DOB (DOB_{max} unit) (U); 2. the time at DOB_{max} (U/min); 3. the slope of the rising part of the curve (U/min) and 4. the time at 50% of area under curve ($AUC_{50\%}$, min). The DOB_{max} and slope are direct, meanwhile the time at DOB_{max} and the time at $AUC_{50\%}$ are inversely proportional to gastric emptying (Debreceni et al., 1999; Mózsik et al., 2004a).

2.9. Sugar loading test in healthy human subjects

The glucose (75 g) was orally given in 100 mL water. The plasma level of glucose was measured enzymatical (Boehringer, Germany). The plasma levels of insulin (μIU/mL) (Biochem Immunsystem), C peptide and glucagon (pg/mL) (Byk-Sangtect Diagnostic GmbH) were measured by RIA. The all measurements were carried out before and after administration repeatedly in every 15 mins for 4 h period (Dömötör et al., 2006b).

2.10. Immunohistochemical examinations in the gastric and large bowel mucosa in patients with various disorders

The classical pathological histological examinations were carried out by an independent pathologist for giving the histopathological diagnosis of patients (besides the classical laboratory, iconographic examinations).

The specific immunohistochemical examinations were used for the same biopsy specimens used for pathological examination. Specific antisera were used for detection of vanilloid (TRVP1) receptor (polyclonal anti-TRVP1, Abcam, Cambridge, UK), CGRP (polyclonal anti-CGRP, Abcam, Cambridge, UK) and SP (monoclonal anti SP, Abcam, Cambridge, UK).

The TRVP1 and CGRP positive and/or negativity was detected, meanwhile SP staining was evaluated by a semi-quantitave scale (Dömötör et. al., 2005).

2.11. Detection of Helicobacter pylori in patients with chronic gastritis

The presence of H. pylori was detected by ^{13}C-urea breath test (Izinta, Hungary) and with specific histological staining of biopsy specimens. The diagnosis of chronic gastritis was based on the classical pathological histology. The results of observations were expressed as means ± SEM. The unpaired and paired Student's *t* tests were used for the calculation of results between the identical observations. P value ≤ 0.05 was considered statistically significant.

2.12. Evaluation of capsaicin-stimulated gastric mucosal protection on IND-induced gastric microbleeding and capsaicin-produced gastric mucosal protection on the IND-induced gastric microbleeding before and after 2 weeks capsaicin treatment (based on randomized, prospective and multi-clinical study in healthy subjects) (Mózsik et al., 2004 a; 2005; 2007)

2.12.1. Measurement of gastric microbleeding before and after 2 weeks capsaicin treatment

The baseline in gastric microbleeding was measured and carried out as those under the point of 7.1. The gastric microbleeding was expressed in mL/ day (means ±SEM).

2.12.2. Measurement of IND-induced acute gastric microbleeding before and after 2-week capsaicin treatment

These measurements were carried out in healthy human subjects as those were written under 7.2. These healthy subjects received 3x25 mg IND for one day and 25 mg IND on the next day before the measurement of the extent of gastric microbleeding. The gastric microbleeding was expressed in mL/day (means ±SEM).

2.12.3. Measurement of capsaicin-induced acute gastric mucosal protection against the IND-induced acute gastric microbleeding before and after 2-week capsaicin treatment

The observations were carried out under the observational circumstances mentioned in 12.2, however, different doses of capsaicin (200 and 400 μg given orally) were used. Two hundred and 400 μg capsaicin were applied given orally before the measurement of IND-induced acute gastric microbleeding before and after 2-week capsaicin treatment.

2.12.4. Evaluation of capsaicin's effect by randomized, prospective, multi-clinical studies in patients with chronic Helicobacter pylori positive gastritis before and after eradication treatment to capsaicin-effect due to stimulation of capsaicin-sensitive neural afferentation (Lakner et al 2011)

These studies were carried out in 38 persons (including 20 healthy persons and 18 patients with H. pylori positive gastritis). The histologically normal controls were in ages: 41 to 67 years, mean: 52.1 years), meanwhile the ages of patients with chronic Helicobacter pylori infection were 39 to 68 years, mean: 56.4 years) (Lakner et al., 2011).

The presence of H. pylori was determined by the methods mentioned above.

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The eradication therapy was involved a seven days treatment with double dose proton-pump inhibitor consisting of PPI (pantoprazole 2x40 mg/day), amoxicillin (1000 mg twice daily) and clarithromycin (500 mg twice daily), according to European guidelines (Malfertheiner et al., 2007). Following this one week of eradication period, the patients further treated with normal dose of PPI for other another week.

The gastroscopies, gastric biopsies, general and special immuno-histochemical examinations were carried out at the time of entry of patients into the eradication treatment, after the eradication treatment (Lakner et al., 2011).

2.13. Used drugs and compounds

Anticholinergic (atropine, Egis, Budapest, Hungary), antimuscarinic (Pirenzepine, Boehringer, Ingelheim, Germany) agents; [histamine H_2-receptor antagonists (Cimetidine, Pannon-Pharma, Hungary), ranitidine (Biogal-Teva, Hungary), famotidine (Richter Gedeon, Hungary)], proton pump inhibitors (PPI) [(Omeprazole, Astra-Zeneca, Sweden), Esomeprazole (Astra-Zeneca, Sweden)]; indomethacin (Chinoin, Budapest, Hungary) were used.

Capsaicin was applied in these studies obtained from Asian Herbex Ltd: Capsaicin USP as manufactured in Andhra Pradesh, India). The Drug Master File (DMF) is signed in the documentation of Drug and Food Administration (FDA) in the United States as only one capsaicin preparation for orally applicable preparate (" 17856 A II 26.10.2004 Asian Herbex Ltd. : Capsaicin USP as manufactured in Andhra Pradesh, India") (for further details, see Mózsik et al. 2009b).

2.14. Statistical evaluation of results

The results were expressed as means ± SEM. The paired and unpaired Student's t test and ANOVA test were used for the statistical analysis of the results. The results were taken to be significant when the P value was found ≤ 0.05. Special mathematical programs were applied for the evaluation of results of human phase I. examinations.

3. Results

3.1. Capsaicin-induced BAO in healthy human subjects

The capsaicin (given in doses of 100, 200,400 and 800 μg orally) dose-dependently inhibited the gastric acid output (Y=-0.13.X+1.164; r=0.97; n=16; $P < 0.001$) (Mózsik et al., 1999; Mózsik et al., 2005). The ED_{50} value of capsaicin was obtained as 400 μg/person on the gastric BAO (in case of administration of capsaicin in doses which stimulates the capsaicin-sensitive afferent nerves) (Figures 1 and 2) (Mózsik et al., 1999; 2005).

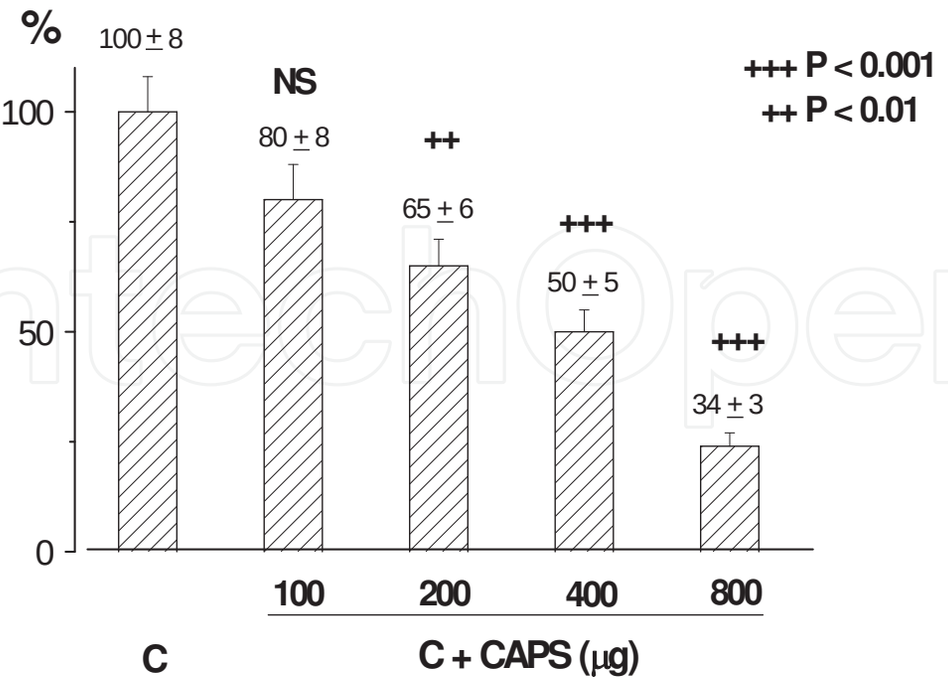

Figure 1. Capsaicin-induced inhibition on gastric basal acid output (BAO) in 16 human healthy subject. The results were expressed as per cent of untreated (control) group (means±SEM). The results of the mathematical analysis were expressed as control vs. capsaicin treated groups. Abbreviations: NS=not significant;++=P<0.01;+++=P<0.001 (Mózsik et al., J Physiol Paris 93:433-436, 1999).

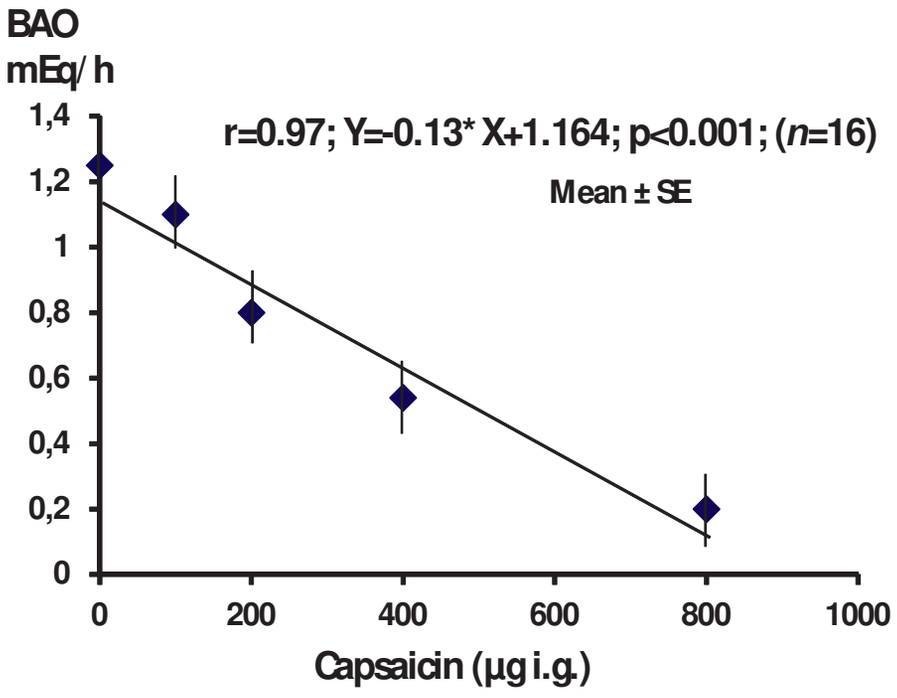

Figure 2. Inhibition of gastric acid basal output (BAO) by capsaicin in 16 healthy human subjects (after Mózsik et al.: World J Gastroenterol 11: 5180-83, 2005).

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3.2. Affinity and intrinsic affinity curves for the capsaicin, muscarinic agents, H_2-receptor antagonists and proton pump inhibitors on BAO in healthy human subjects

The action of the compounds inhibiting the gastric basal acid secretion is presented by Figure 3. The curve indicates that no competitive actions of these drugs exist on the gastric basal acid output. The pD_2 values were calculated from the affinity curves obtained in the molecular pharmacological studies.

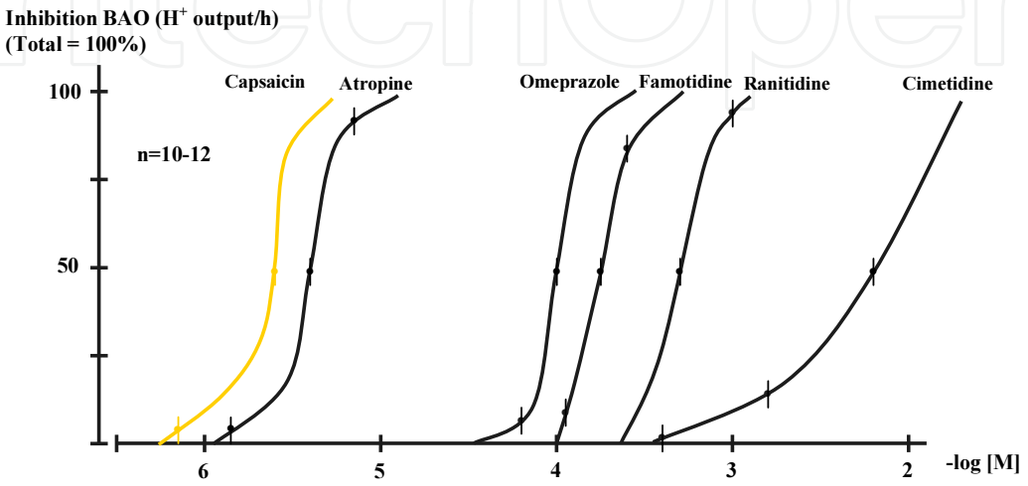

Figure 3. Affinity curves for drugs inhibitory actions of different antisecretory drugs on the gastric basal acid output (BAO) in human healthy subjects. The absolute values were calculated as H^+output/h, the presentations of curves expressed in per cent value (total=100%) (means ±SEM). (After Mózsik et al.: Inflammopharmacology 15: 232-45, 2007)

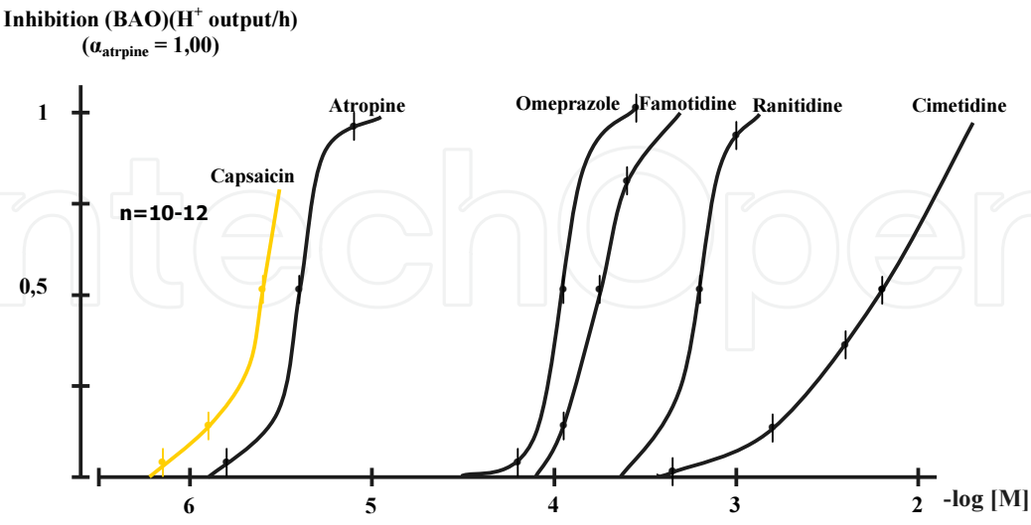

Figure 4. Intrinsic activity curves for the inhibitory drugs of different antisecretory drugs and capsaicin (given in stimulatory doses of capsaicin-sensitive afferent nerves) on the gastric acid basal output (BAO) in human healthy subjects, which were expressed to action of atropine (1.00) (α atropine) (means ±SEM). (After Mózsik et al.: Inflammopharmacology 15: 232-45, 2007).

The intrinsic activity curves for the drugs inhibiting the gastric basal acid outputs in healthy human subjects were calculated. The intrinsic activity ($\alpha_{atropine}$=1.00) was taken to be equal to 1.00, and the values for other drugs were expressed to action of atropine (Figure 4). The pA_2 values (50 % inhibition of intrinsic activity in [-] molar values) were calculated from the intrinsic activity curves.

For the molecular pharmacological understanding the background of the action of drugs, action the molecular weights, pD_2 values, of the intrinsic activity (in comparison to atropine action) and pA_2 values were calculated and presented in Table 1.

Compounds	M.W.	pD_2	Intrinsic activity	pA_2
Capsaicin	305,4	5,88	0,76	5,87
Atropine	289,38	5,40	1,00	5,40
Pirenzepine	424,34	3,93	0,89	3,93
Cimetidine	252,34	2,23	1,00	2,23
Ranitidine	314,41	3,33	1,00	3,33
Famotidine	337,43	3,77	1,00	3,77
Nizatidine	331,47	3,34	1,00	3,34
Omeprazole	345,42	3,97	1,00	3,97
Esomeprazole	345,42	3,97	1,00	3,97

Table 1. Summary of the affinity (pD_2) and intrinsic activity (expressed in value of $\alpha_{atropine}$=1,00)(pA_2) values of capsaicin, atropine, Pirenzepine, cimetidine, ranitidine, famotidine, Omeprazole and Esomeprazole on the gastric basal acid output (BAO) in healthy human subjects. (After Mózsik et al.: Inflammopharrmacology 15:232-45, 2007)

The Figures 3, 4 and Table 1 clearly indicate that the capsaicin acts in the smaller doses as those drugs acting on the muscarinic (atropine, Pirenzepine), H_2R receptor antagonists (cimetidine, ranitidine, fomatidine, nizatidine) and proton pump inhibitors (Omeprazole, Esomeprazole).

3.3. Changes in the „parietal" and „non-parietal" components of gastric secretory responses in healthy human subjects

The measurements of cations (H^+, sodium, potassium, calcium, magnesium) and of chloride offered the possibility to identify the „parietal" and „non-parietal" components of gastric secretion in humans without and with administration of different drugs (or compounds) (Hollander, 1934).

Using the Hollander's method for the calculation and evaluation of cations, chloride in the gastric juice indicated clearly the significant decrease of „parietal component" (Δ-18±2 mmol/L, P< 0.001) in association with significant increase of „ non-parietal component" (Δ+19±2 mmol/L, $P < 0.001$) of the gastric secretion after application of 400 μg (given orally) of capsaicin (n=10) (Mózsik et al., 2005).

H^+		Na^+		K^+		Ca^{2+}		Mg^{2+}	
A	B	A	B	A	B	A	B	A	B
43±3	25±1	73±4	89±2	13±1	8±0,6	0,98± 0,02	0,88± 0,01	0,49± 0,01	0,38± 0,01
P<0.001		P<0.001		P<0.001		P<0.001		P<0.001	
100±7	58±2	100±5	122±3	100±8	62±5	100±2	90±1	100±2	78±2
"parietal" component				**"non-parietal" component**				**albumin (g/L)**	
A		B		A		B		A	B
43±3		25±2		126±4		145±4		1,23±0,001	1,650 ±0.02
P<0.001				P<0.001				P<0.001	
100±7		58±5		100±3		115±3		100±1	131±2

Table 2. Chemical composition of gastric juice without (A) and with (B) application of capsaicin (ED_{50}=400 μg orally give) in healthy human subjects. The results are given as mmol/L or % (means ±SEM) (n=10). (After Mózsik et al.: World J Gastroenterol 11: 5080-84, 2005)

3.4. Changes of albumin level in the gastric juice after capsaicin administration in healthy human subjects

The albumin concentration increased from 1.24 ± 0.001 g/L vs. 1.63 ± 0.02 g/L (P < 0.001; n=10) after 400 μg capsaicin (i.e. given) application (Mózsik et al., 2005).

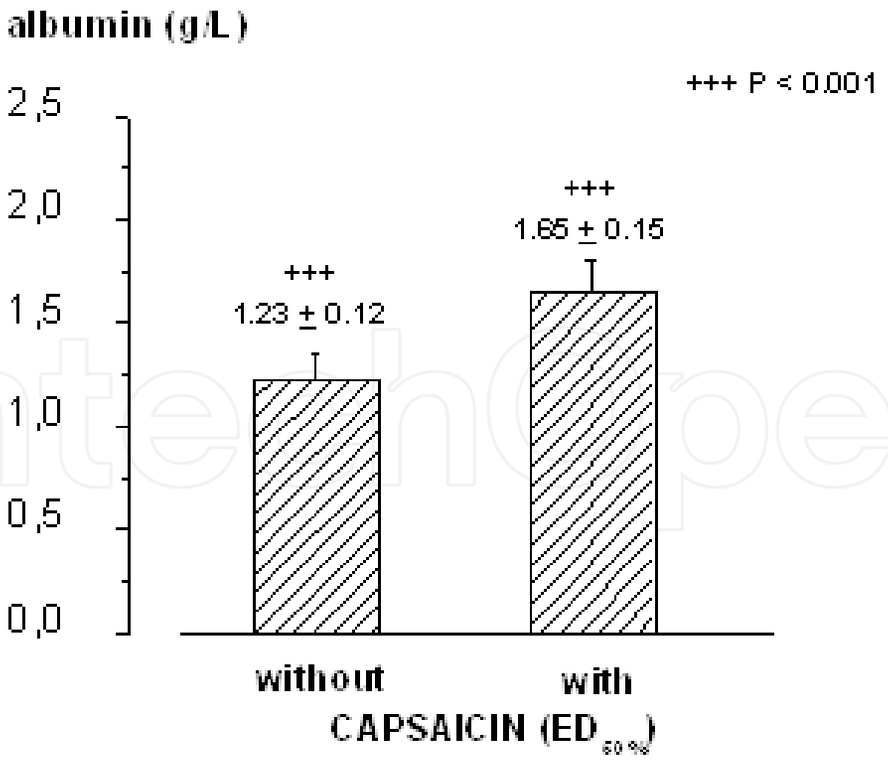

Figure 5. Changes in gastric mucosal proteins (albumin) in the gastric basal output (BAO), without and with capsaicin, in 10 healthy subjects (g/L) (means±SEM).

3.5. Action of capsaicin on the GTPD in the healthy human subjects

The capsaicin (given ig. in doses of 100, 200, 400 and 800 μg) dose-dependently increased the GTPD alone [Δ value from to baseline 10 (-mV)] (Mózsik et al., 2005).

When we applied capsaicin in double dose (800 μg intragastrically given) than we received the same increase in GTPD at the same time period (Hossenbocus et al., 1975; Mózsik et al., 2005) (Figure 6).

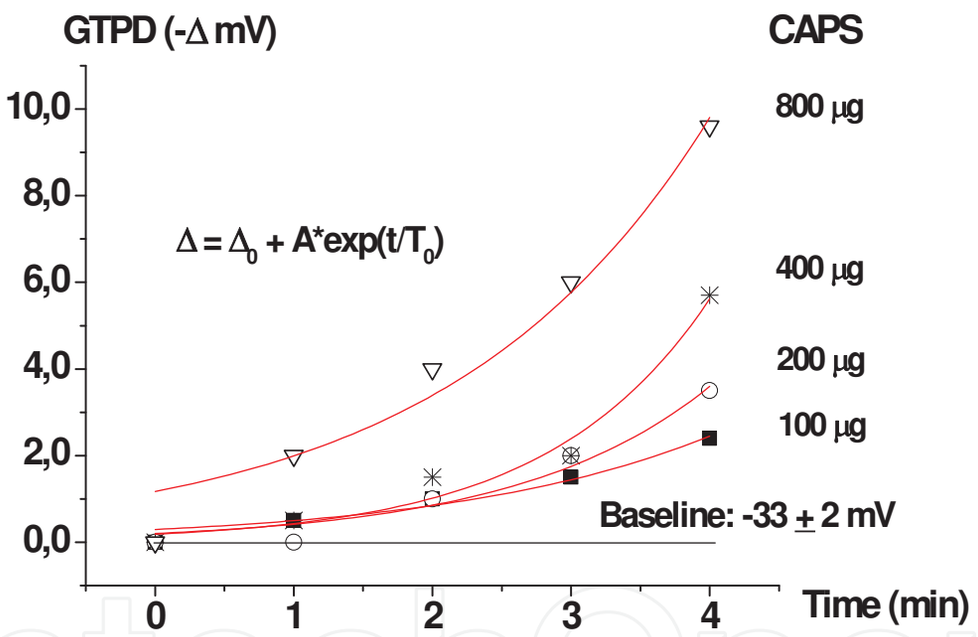

Figure 6. Capsaicin (CAPS) dose-dependent gastric mucosal protective effect of capsaicin on gastric transmucosal potential difference (GTPD) in 10 healthy subjects (after Mózsik et al., World J Gastroenterol 11:5180-5184, 2005).

3.6. Action of ethanol on GTPD in healthy human subjects

The intragastrically applied ethanol immediately and significantly decreased the GTPD [Δ 25 (-mV)] (Mózsik et al., 2005).

3.7. Preventive action of capsaicin on the ethanol-induced decrease of GTPD in healthy human subjects

The intragastrically applied capsaicin (given in doses of 100, 200, 400 and 800 μg) dose-dependently prevented the ethanol-induced decrease of GTPD in human healthy subjects (Mózsik et al., 2003; 2005).

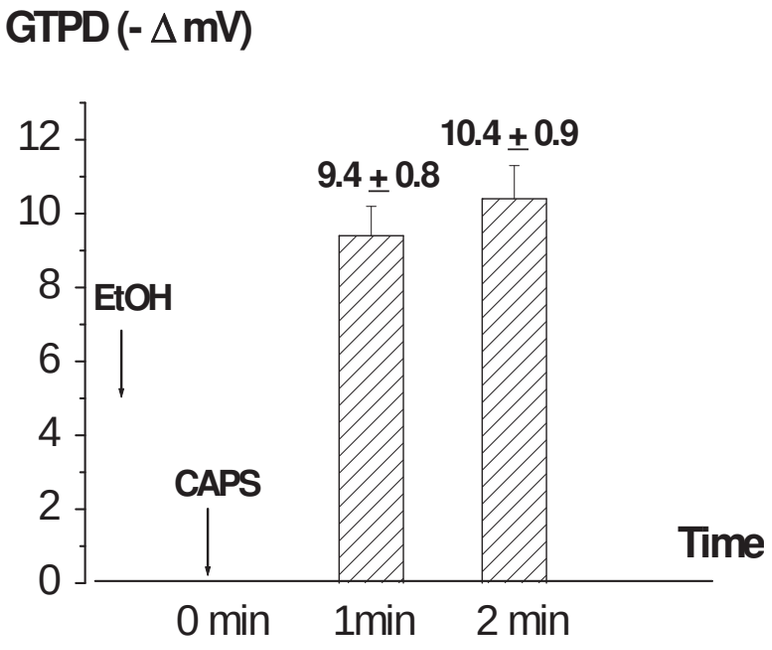

Figure 7. The ethanol (30 v/v in 5 ml intragastrically given) immediately the GTPD in the gastric mucosal surface (in comparison to baseline) (means±SEM) (n=14) (after Mózsik et al., World J Gastroenterol 11:5180-5184, 2005).

3.8. IND-induced acute gastric microbleeding and the acute gastric mucosal preventive effect of capsaicin on the IND-induced acute gastric mucosal damage in healthy human subjects (based on the results of prospective, randomized and multi-clinical study)

3.8.1. Extent of IND-induced acute gastric mucosal damage in healthy human subjects

The baseline of blood losing was 2.0 ± 0.2 mL/ day (n=14) without application of IND, which was increased to 8.1 ± 0.2 mL/day (n= 14; P< 0.001) after application of indomethacin.

3.8.2. Gastric mucosal preventive effect of capsaicin on the IND-induced acute gastric microbleeding in healthy human subjects

The capsaicin was given in doses of 200, 400 and 800 μg orally before the administration of indomethacin. The acutely applied capsaicin prevented by dose-dependent manner of IND-induced gastric microbleeding in healthy human subjects (Y=-0.0071*X+7.78; r=-0.98, n=14; *P*< 0.001) (Mózsik et al., 2005; Sarlós et al., 2003).

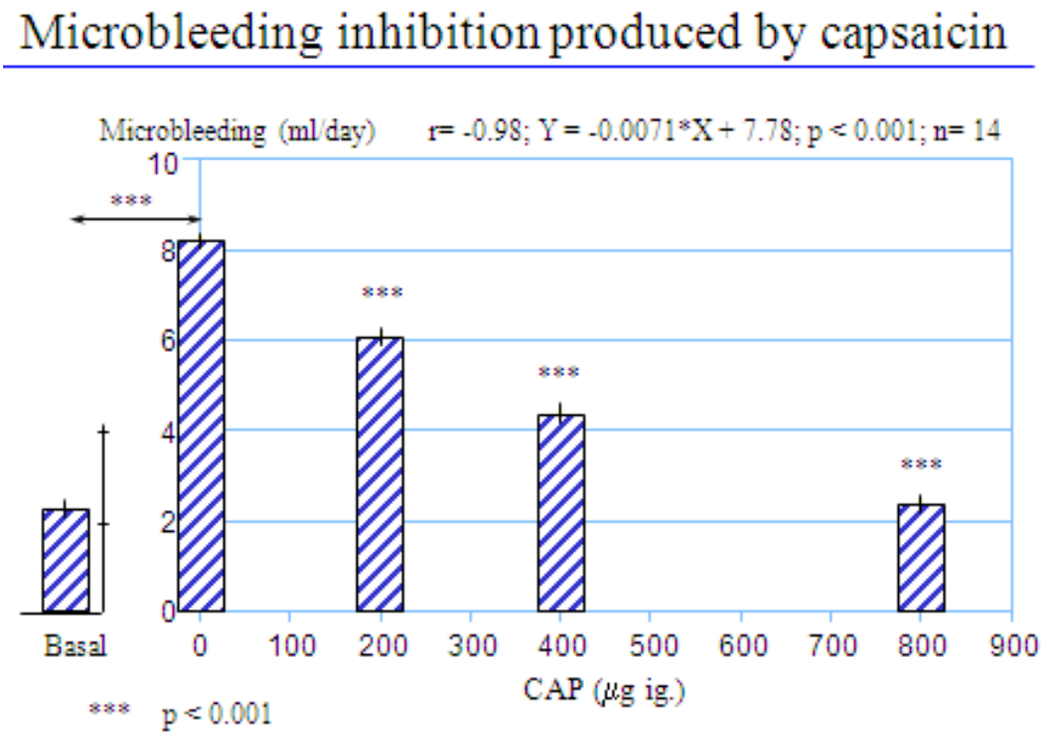

Figure 8. Gastric mucosal protection demonstrated by reduced microbleeding after capsaicin treatment of indomethacin (IND)-induced mucosal damage. (After Mózsik et al.: World J Gastroenterol 11.5180-83, 2005).

3.9. Effect of capsaicin on the gastric emptying in healthy human subjects

The capsaicin was intragastrically given in dose of ED_{50}, which increased significantly the gastric acid emptying: 1. Capsaicin (400 μg, ig=ED_{50})-induced changes in the maximal values of DOB_{max} decreased from 18±1 to 14±1 U (*P<0.01*); 2. the time to reach the DOB_{max} decreased from 148±13 to 70±12 min (*P<0.01*); 3. the slope (in U/min) increased from 0.11±0.01 to 14±0.001 (*P<0.001*); 4. the time to reach the AUC_{50} decreased from 115±10 to 80±8 (min) (n=10; P<0.01) (Debreceni et al., 1999).

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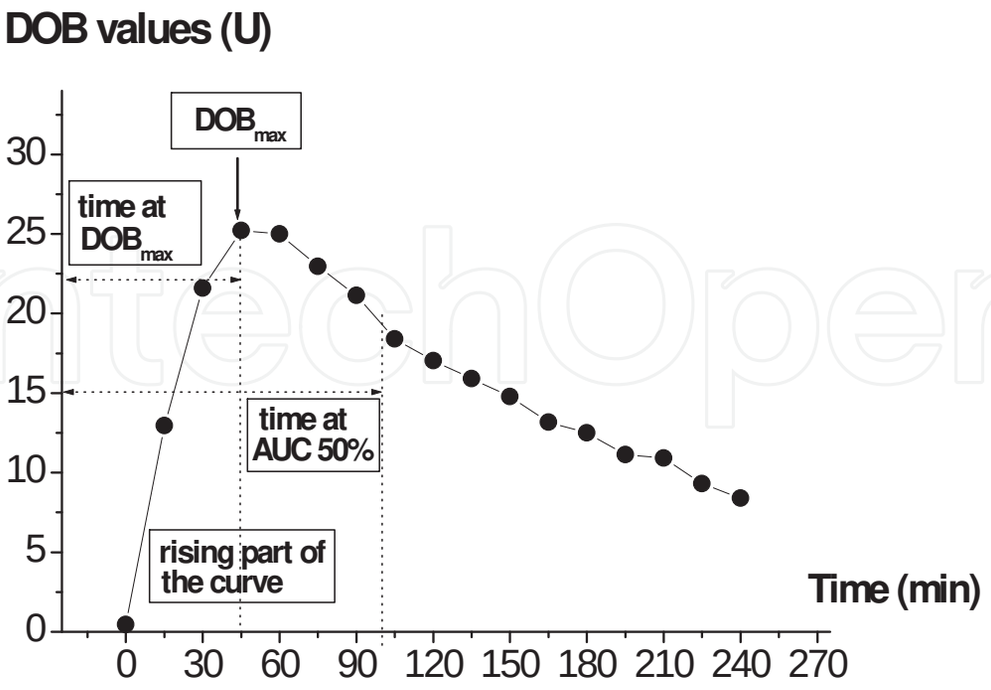

Figure 9. Typical curce obtained by the IRIS (infra-red-spectocsopy) measurement and calculated the delta over base (DOB) value. This value is directly proportional to ratio of $^{13}CO_2$ and $^{12}CO_2$ (DOB~$^{13}CO_2/^{12}CO_2$) in the air sample (Debreceni et al., J Physiol Paris 93: 455-460, 1999).

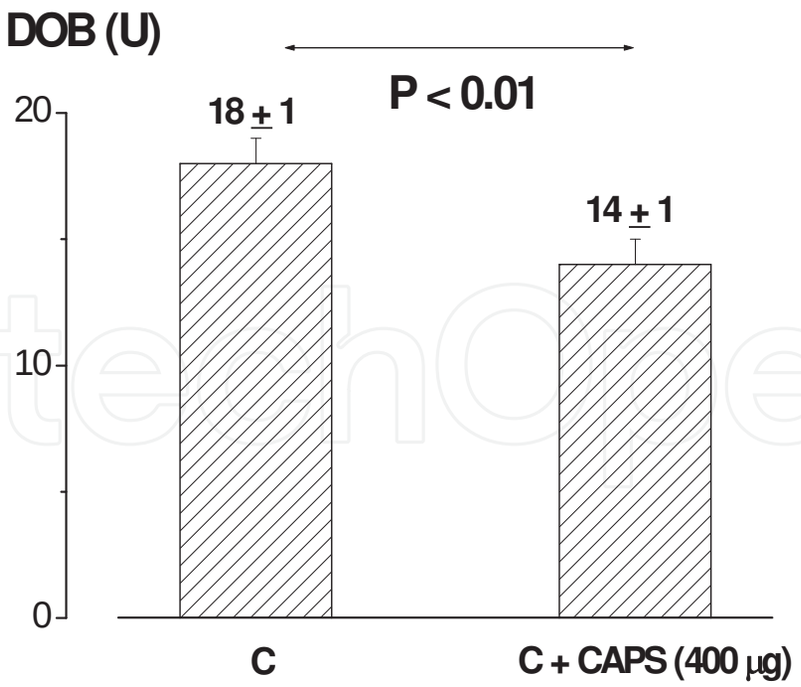

Figure 10. Capsaicin (400 μg ig.given)-induced changes in the maximal values of Delta Over Base (DOB max) (U) in 14 human healthy subjects (means±SEM) (Debreceni et al., J Physiol Paris 93:455-460, 1999).

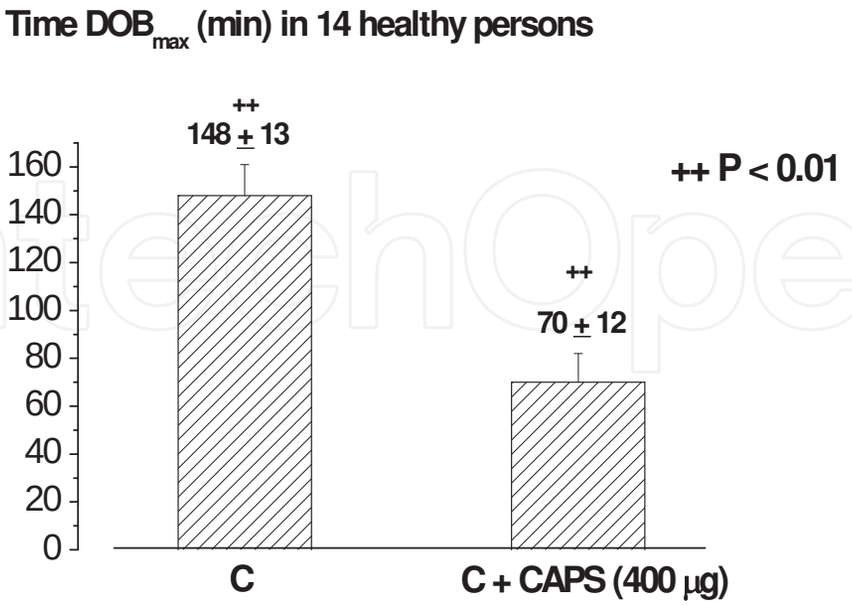

Figure 11. Capsaicin (400 μg ig. given)-induced changes in time to reach the value of DOB $_{max}$ (min) in 14 human healthy subjects (means±SEM) (Debreceni et al., J Physiol Paris 93:455-460, 1999).

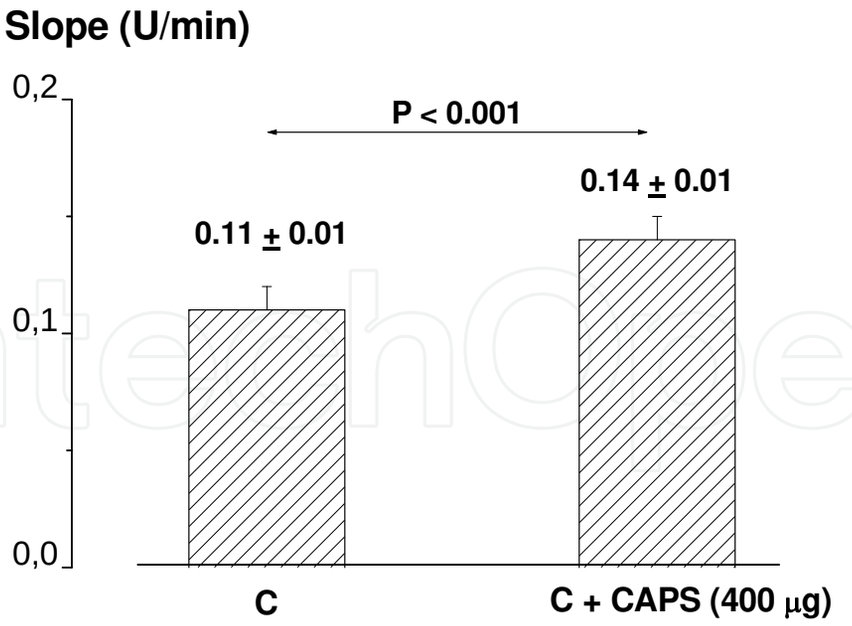

Figure 12. Capsaicin (400 μg ig. given)-induced changes in the slope in its rising part in 14 human healthy subjects (means±SEM) (Debreceni et al., J Physiol Paris 93:455-460, 1999).

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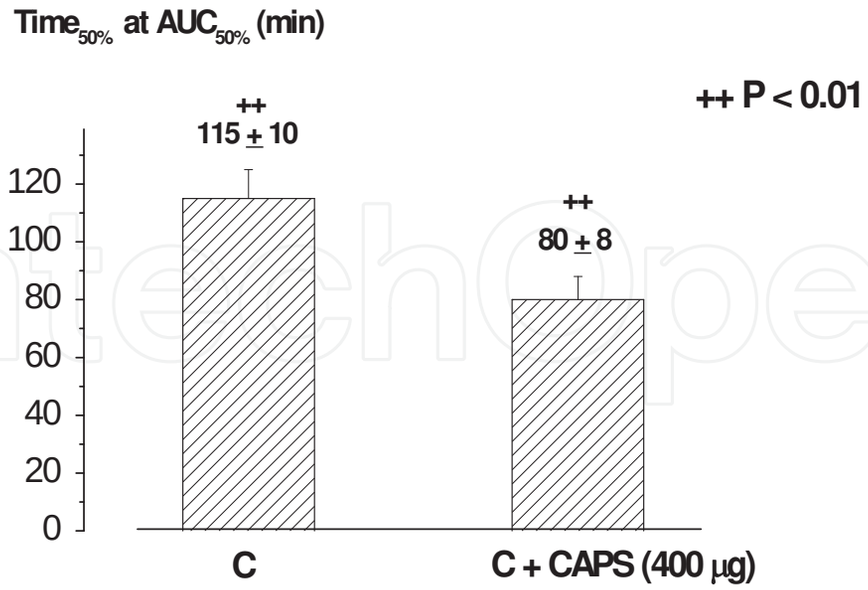

Figure 13. The time of 50% (in min) to rearch the **AUC** $_{50\%}$ in 14 healthy subjects (means±SEM) (U/min) in 14 human healthy subjects means±SEM) (Debreceni et al., J Physiol Paris 93:455-460, 1999).

3.10. Increased glucose absorption from small intestine and of glucagon release by capsaicin during the glucose loading test in healthy human subjects

During glucose loading test we measured the glucose absorption in the proximal part of the small intestine, insulin, C peptide, glucagon using the plasma level of glucose as markers substance (Dömötör et al., 2006).

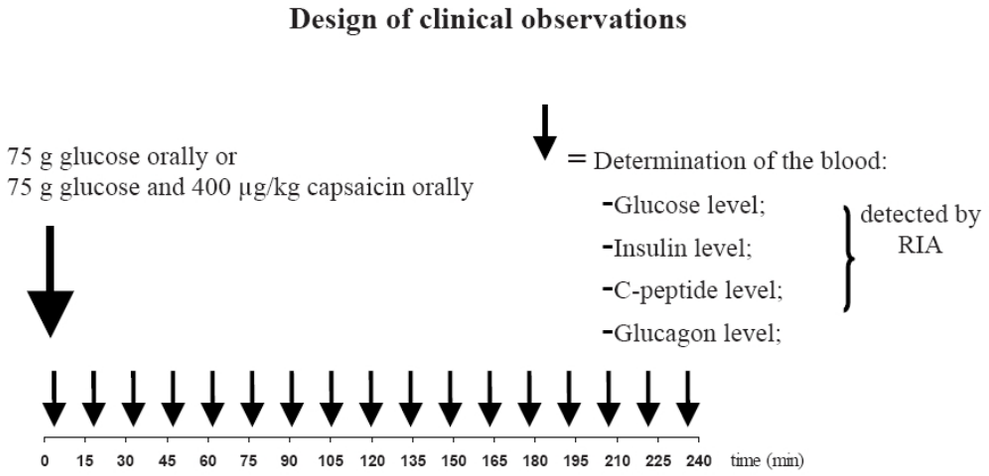

Figure 14. Design of clinical observations with glucose observation and utilization in 14 healthy human subjects without and with (400 μg, $ED_{50,}$ orally given) capsaicin application. The measurement of glucose, insulin, C-peptide, glucagon was carried out from the plasma level in every 15 min period from the glucose application to 4 h. (After Mózsik et al.: Inflammopharmacology 15:232-45, 2007).

The absorption of glucose from the small intestine and glucagon release increased by capsaicin administration; however no significant changes were obtained in neither insulin nor C peptide release under these observational circumstances (Figure 15).

The plasma levels of glucose increased significantly 30 to 150 min and the plasma level of glucagon increased from 90 to 180 min after capsaicin administration in human healthy subjects given 75 g glucose orally. The plasma levels of insulin and C peptide increased from 75 to 165 min after glucose administration; however, levels did not differ significantly.

3.11. Results of the immunohistochemical examinations in the human gastric and large bowel mucosa in healthy human subjects and in patients with different gastrointestinal disorders

3.11.1. Demonstration of capsaicin receptors, CGRP and SP in the human gastric and large bowel mucosa in healthy human subjects

The results of these observations were obtained in „ healthy human subjects", who had different functional complaints and the endoscopic examinations were carried out to exclude the presence of any histologically proven disease (the clinical histological examinations were carried out by the independent pathologist) and the opinion of pathologist gave normal histology.

The immunohistochemical examination demonstrated the presence of capsaicin (TRVP1) receptors in the gastric and large bowel mucosa obtained from biopsy samples. The location of capsaicin receptor could be demonstrated near the nerve endings, vascular vessel and in the epithelial layer (Figure 16) (Dömötör et al., 2005).The CGRP and SP could be observed in gastric mucosa and these parts of large bowel mucosa as well (Figure 17) (Dömötör et al., 2005).

3.11.2. Demonstration of capsaicin receptor, CGRP and SP in the gastric and large bowel mucosa in patients with different disorders

The preliminary results of these observations were published by Dömötör et al. (2005).

These patients went over the clinical endoscopic and pathological examinations. The original pathological diagnosis was given by an independent pathologist.

The capsaicin receptor, and released neuropeptides (CGRP and SP) could be detected in all types of patients with different disorders (Table 3). The results of these preliminary clearly indicated the following: 1. capsaicin could be demonstrated in patients with superficial gastritis, erosive gastritis, stomach polyps, stomach cancer, inflammation of large bowel disease, colon polyps with severe dysplasia and colorectal cancers.

The CGRP could be demonstrated in most of the all of the above mentioned diseases; meanwhile the SP could not be demonstrated in these diseases (Table 3).

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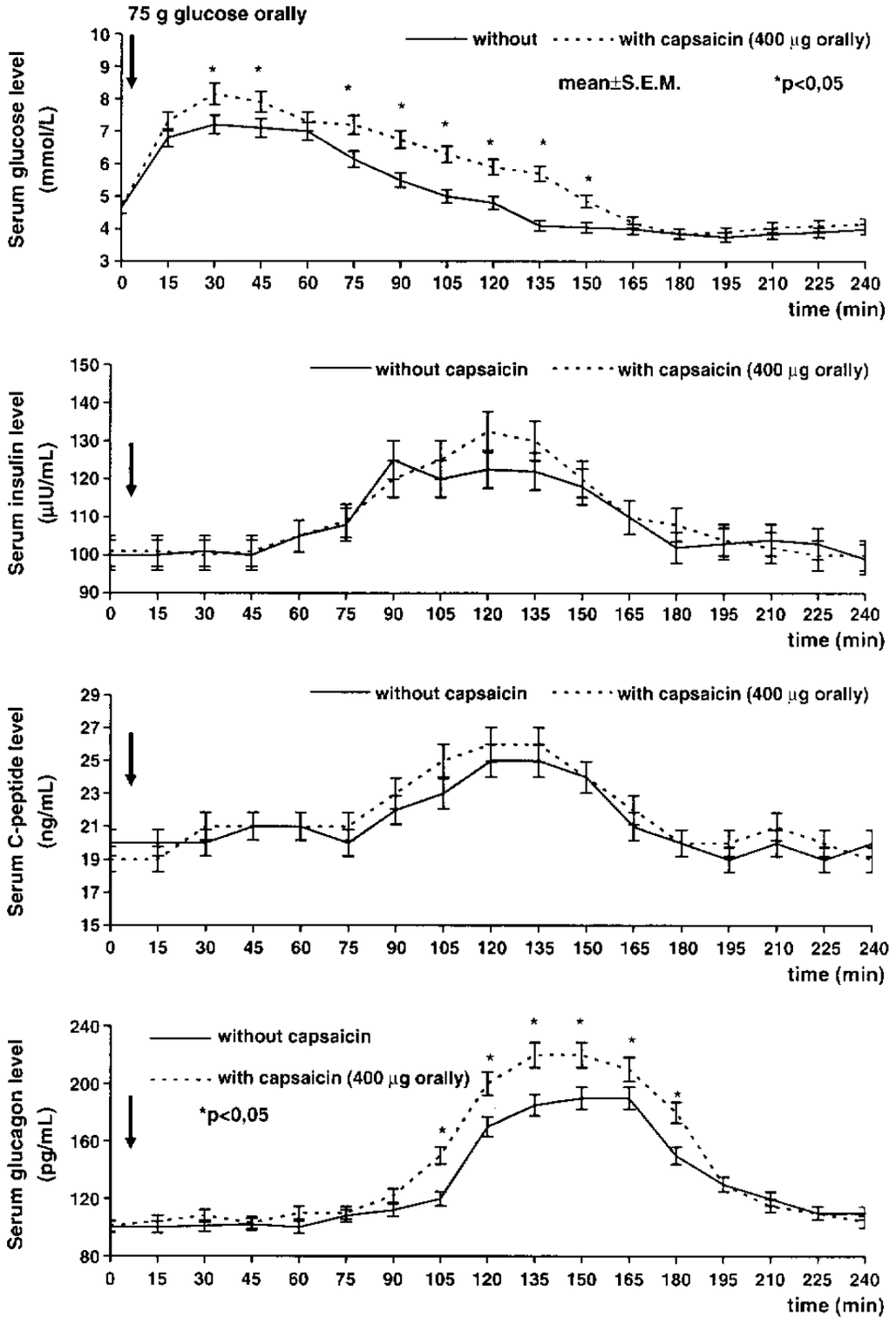

Figure 15. Changes in plasma level of glucose, insulin, C-peptide and glucagon after oral administration of glucose (75 g in 100 ml water) in 14 healthy human subjects. Capsaicin (400 μg) was orally given in gelatine capsule (Hungaropharma, Budapest, Hungary). The plasma levels of glucose, insulin, C-peptide and glucagon were measured every 15 min for 4 h. The results are expressed as means ±SEM. (After Dömötör et al.: Eur J Pharmacol 534: 280-83, 2006).

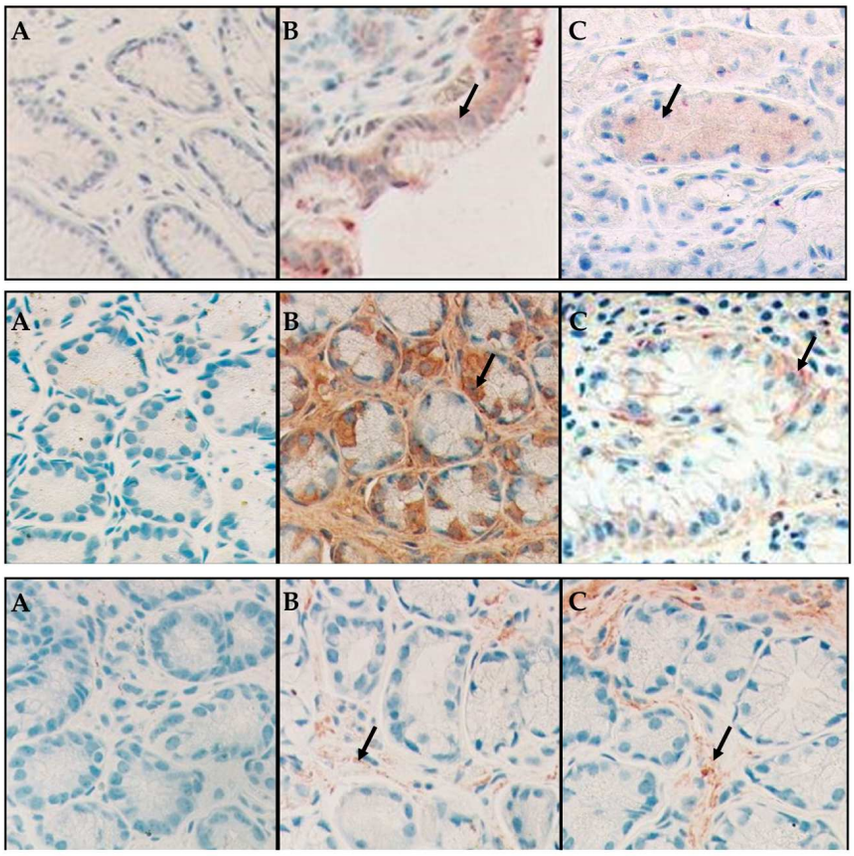

Figure 16. The immundistribution of TRPV1 (first row), CGRP (second row) and of SP (third row) in the gastric mucosa of a healthy subject (A) and of patient with H. pylori negative (B) and H. pylori positive (C) chronic gastritis. Arrows show the immunsigns in the mucosa. (After Mózsik et al.: Inflammopharmacology 15: 232-45, 2007).

STOMACH	TRPV1	CGRP	SP
Superficial gastritis	+	+	-
Erosive gastritis	+	+	-
Gastric ulcer	-/+	-/+	-/+
Polyp	+	+	-
Carcinoma	+	+	-
LARGE BOWEL	**TRPV1**	**CGRP**	**SP**
Inflammation	+	+	+
Polyp with moderate dysplasia	-	-	-
Poly with severe dysplasia	+ spot-like	-	-
Carcinoma	+ spot-like	+	-

*The signs of+or – indicate the trend of expression in the specific immunohistochemical examinations in the mucosa specimens (stomach and large bowel) in patient different disease.

Table 3. Immundistribution of capsaicin receptor (TRPV1), calcitonin-gene releted peptide (CGRP) and substance P (SP) in the gastric and large bowel mucosa of patients with different GI disorders. (After Mózsik et al.: Inflammopharmacology 15: 232-45, 2007)*

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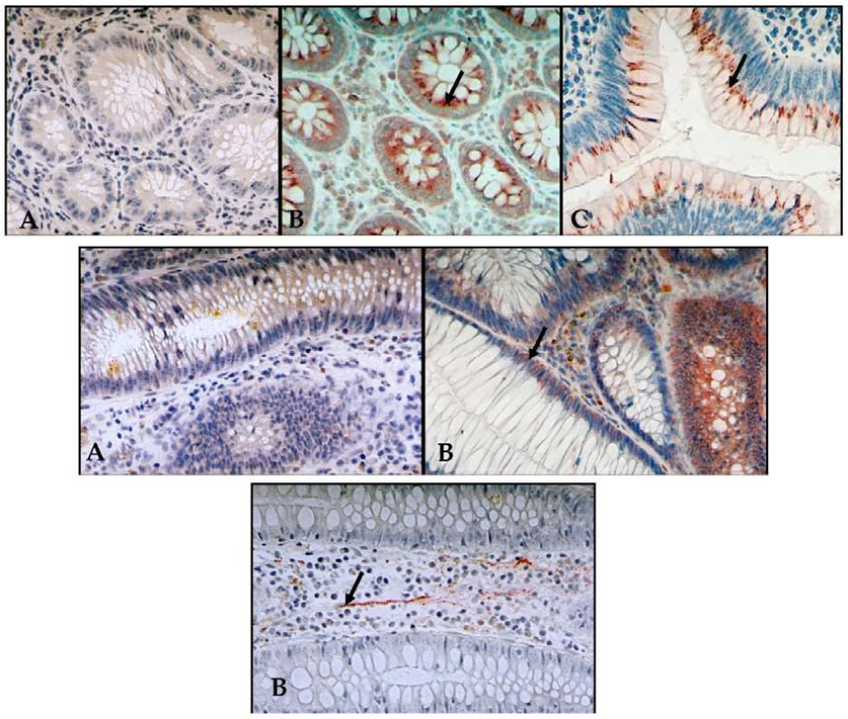

Figure 17. The immundistribution of TRPV1 (first line), CGRP (second line) and of SP (third line) in the colon mucosa of control person (A) and of patient with inflammatory bowel disease (B) and with severe dysplastic polyp (C). Arrows show the immunsigns in the mucosa. (After Mózsik et al.: Inflammopharmacology 15: 232-45, 2007)

3.12. Capsaicin receptor, CGRP and SP in the patients with Helicobacter positive and negative chronic gastritis

These observations were carried out in 57 patients with chronic gastritis (21 patients from them were H. pylori positive and 30 patients were H. pylori negative).

The expression of capsaicin receptors and CGRP increased in the gastric mucosa with both bacteria positive and negative chronic gastritis, meanwhile SP increased with a limited extent Determined by a semi quantitative scale (Dömötör et al., 2006a). The expression of TRVP1, CGRP, and SP increased significantly in the human gastric mucosa with chronic gastritis; however, no difference was obtained in their expression in patients with H. pylori positive and negative chronic gastritis (Dömötör et al., 2006a).

3.13. Measurements of the gastric microbleeding before and after 2-week capsaicin treatment: Testing of the changes in baseline, IND-induced acute gastric microbleeding and of capsaicin-stimulated gastric mucosal protective effect on the IND-induced acute gastric microbleeding in healthy human subjects (Figures 18 and 19)

3.13.1. Baseline before and after 2 weeks IND treatment without application of any drug and/or compound

The baseline of gastric microbleeding was detected 2.1 ± 0.1 vs. 2.0± 0.1 mL/day, before and after 2 weeks capsaicin treatment (without other drug /compound application).

3.13.2. Measurement of IND-induced acute gastric mucosal microbleeding – before and after 2 weeks capsaicin treatment – in healthy human subjects

The acute administration of IND significantly increased the extent of gastric microbleeding vs. baseline (without administration of IND) (*P<0.001*; n=14) in healthy human subjects before (baseline vs. IND., 2.1 ± 0.1 vs. 8.3 ± 0.2 mL/day) and after (baseline vs. IND., 2.0± 0.1 vs 7.8±0.3 mL/ day) 2 weeks capsaicin (3 x 400 μg orally given) treatment (Mózsik et al., 2005).

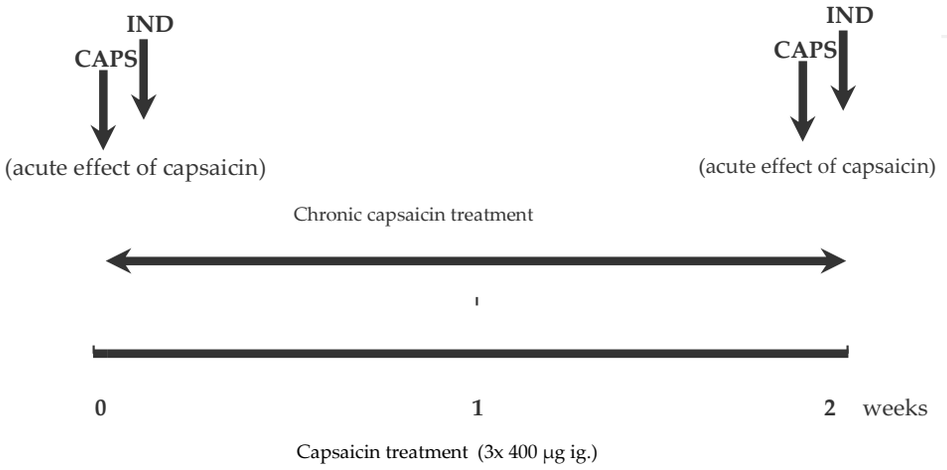

Figure 18. Clinical study design of a chronic capsaicin treatment in human healthy subjects. Abbreviations: CAPS: capsaicin, IND: indomethacin.

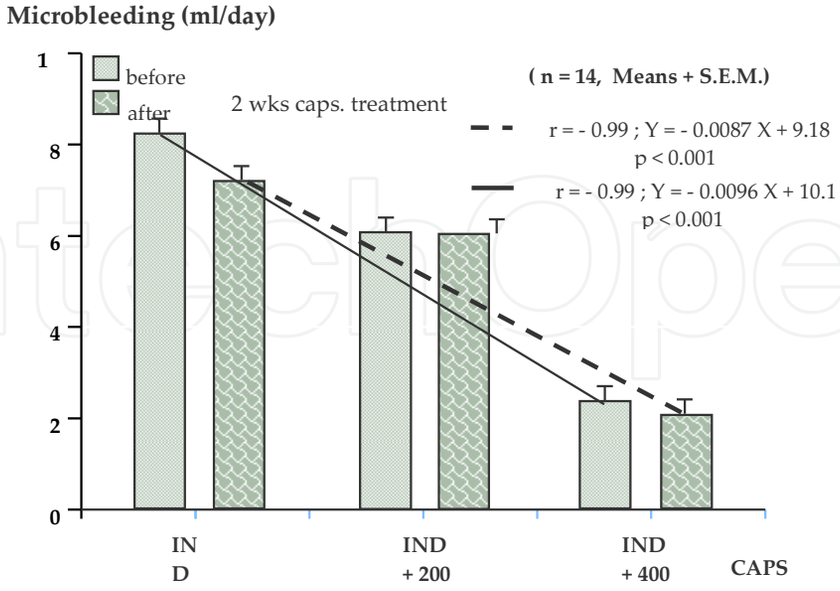

Figure 19. Capsaicin (given 200 and 400 μg ig.)-induced gastric mucosal preventive effects on indomethacin (3x25 mg ig.)-produced gastric mucosal microbleeding before and after a chronic capsaicin (3x400 μg i.g. for 2 weeks) in 14 human healthy subjects. The results were expressed as means ± SEM).

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3.13.3. Measurement of acutely applied capsaicin-induced gastric mucosal protective effect on the IND-induced acute gastric microbleeding before and after 2 weeks capsaicin treatment in healthy human subjects

The intragastrically applied capsaicin dose–dependently prevented the IND-induced gastric mucosal damage (Mózsik et al., 2003; 2004a; 2005) – before (Y=-0.0087X+9.18, r=-0.99: *P<0.001*) and after (Y=-0.0096 X+10.1 ; r=-.0.99 ; *P<0.001*) 2 weeks capsaicin treatment – when the capsaicin was acutely and intragastrically given (in doses of 200 and 400 μg) before the one day IND treatment (see the description in the methods) (Mózsik et al., 2005).

3.14. Expression of capsaicin receptor, CGRP, and SP in patients with chronic gastritis

3.14.1. Capsaicin-sensitive afferentation in H. pylori positive and negative chronic gastritis

The symptoms of patient's suffering from chronic gastritis with or without H. pylori infection (20 H. pylori positive and 30 H. pylori negative) were nonspecific including epigastric discomfort, nausea, loss of appetite and vomiting. The patients underwent physical, laboratory, ultrasonographic, endoscopic and histological (including special immuno-histochemical) examinations. Twenty people with functional dyspepsia (all of them underwent the aforementioned medical, laboratory, iconographic and histological examinations and all of these examinations indicated 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 ten males and ten females in the functional dyspepsia group.

The H. pylori infection was detected by ^{14}C urea breath test, rapid urease test, Warthinn-Starry silver staining and other specific histological examinations. The gastric tissue samples from the stomach and antrum were examined by an independent histologist and classified of chronic gastritis according to the Sydney System.

The immuno-histochemical 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 monoclonal antibody, the TRPV1 receptor and CGRP were labeled using polyclonal rabbit antisera (all from Alcam Ltd., UK, Cambridge).

3.14.2. Capsaicin-sensitive afferentation in 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 41 to 67 years (mean=52.2 years). The age of patients with chronic H. pylori positive gastritis (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 after the starting of the examinations. The biopsies were taken from the corpus and antrum of patients with chronic gastritis, before and after eradication treatment and from healthy subjects.

The H. pylori positive patients underwent 7-day eradication treatment with combination of double dose of PPI (pantoprazole 2x40 mg/ day), amoxicillin (1000 mg twice daily) and clarithromycin (500 mg twice daily) according to the European guidelines. After this one week combination treatment, the patients continued to take normal dose of PPI for another week.

The H. pylori infection was detected before and after treatment. The results of eradication treatment was successful in 89%, the gastric histology (by biopsy and by histology) indicated normal picture in 22% of cases, and 78 % of patients showed moderate gastritis.

The expression of TRPV1 and CGRP increased significantly in the gastric mucosa of patients with chronic gastritis – independently on the presence of H. pylori positive or negative status and of successful eradication treatment in patients with H. pylori positive gastritis), meanwhile no significant expression changes were obtained for SP in the gastric mucosa in these groups) (Dömötör et al., 2005; Lakner et al., 2012, Mózsik et al., 2011; 2013, Czimmer et al., 2013) (Figures 20, 21 and Table 4).

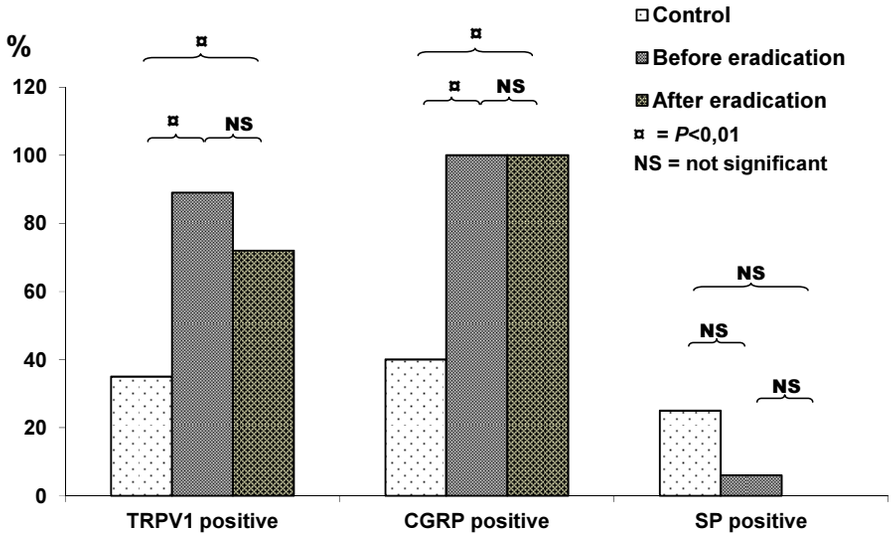

Figure 20. Changes in the immunhistochemical distribution of capsaicin receptor (TRPV1), CGRP and SP in patients with H. pylori positive chronic gastritis before and after eradication therapy. (After Lakner et al., World J Gastrointest Pharmacol Ther. 2: 36-41, 2011)

	TRPV1		CGRP		Substance P	
	Positive	**Negative**	**Positive**	**Negative**	**Positive**	**Negative**
Before eradication	88,89 %	11,11 %	100 %	0 %	5,56 %	94,44 %
(n=18)	(16)	(2)	(18)	(0)	(1)	(17)
After eradication	72,22%	17,78%	100 %	0 %	0 %	100 %
(n=18)	(13)	(5)	(18)	(0)	(0)	(18)
Control group (n=20)	35 % (7)	65 % (13)	40 % (8)	60 % (12)	75 % (15)	25 % (5)

Table 4. The summary of the changes in the immunhistochemical distribution of capsaicin receptor, calcitonin gene-related peptide and substance P in patient with chronic *H. pylori* positive gastritis before and after eradication therapy.

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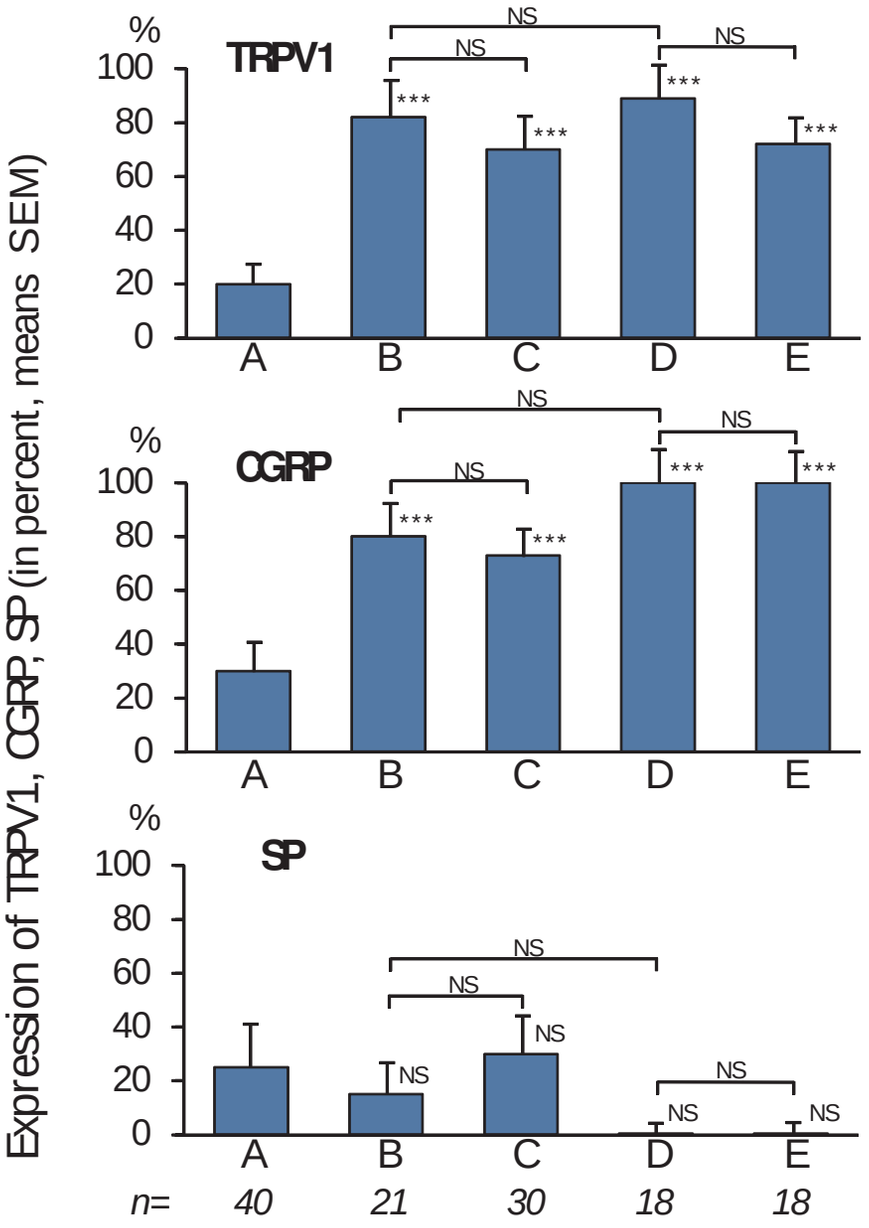

Figure 21. Changes in the expression of capsaicin receptor (TRPV1), calcitonin gene-related peptide (CGRP) and substance P (SP) in the human gastric mucosa of healthy voluntaries (histologically intact) (A), *H. pylori* positive (B), *H. pylori* negative (C) and *H. pylori* positive before (D) and after (E) eradication (pantoprazole 40, amoxicillin 1000 and clarithromycin 500 mg, all two times per day, for seven days) (n=number of patients). (After Mózsik et al., 2014).

4. Discussion

The vagal nerve plays a key role in the gastrointestinal physiology, pathology and pharmacology. The nerve fibres of vagus can be divided into afferent (about 90%) and efferent fibres (10 %) based on animal observations. About 9 per cent of afferent fibres are capsaicin sensitive afferent fibres (Gabella and Pease, 1973; Grijalva and Novin, 1990).

Many observations on the field of Gastroenterology were based on the modification of efferent fibres of vagal nerve, except the classical surgical vagotomy (both in the animal experiments and in human observations with peptic ulcer disease). This standpoint was emphasized during the research period performed by the application of different anticholinergic compounds acting at the level of muscarinic receptor.

Since histamine also plays an essential role in the gastric acid secretion and in many other immunological processes, various H_2 receptor antagonist compounds were developed like cimetidine, ranitidine, famotidine and nizatidine.

After recognition of the H^+-K^+-ATPase as biochemical structure of gastric acid secretion, the so-called proton pump inhibitors (H^+-K^+-ATPase inhibitors) were developed and studied in clinical practice with great efforts (Mózsik, 2006).

The principle problems for clinicians were that the research had not offered any possibilities for studying capsaicin sensitive afferent fibres of vagal nerve in the human physiology, pathology, pharmacology and in human medical therapy. The observations of Jancsó et al. (1967; 1968; 1970) opened a new gate for evaluation of the potential roles of capsaicin sensitive afferent fibres independently from other afferent nerves in various physiological, pharmacological and pathological processes.

Szolcsányi and Barthó (1981) clearly demonstrated the dual actions of capsaicin in peptic ulceration of rat: capsaicin – given in small doses – prevented; meanwhile this compound given in higher doses aggravated peptic ulcer disease in rats. Following them Holzer studied the details of capsaicin actions in the GI tract (see the reviews of Holzer 1998; 1999, 2013; Szolcsányi, 2014).

Our experimental studies with capsaicin have been carried out together with professor Szolcsányi (Department of Pharmacology and Pharmacotherapy, Medical and Health Centre, University of Pécs, Hungary) from 1980, understanding the actions of capsaicin in gastric mucosal damage and protection have been our main focus (Mózsik et al., 1997).

My work team started with the human clinical pharmacological studies from the years of 1960 in patients with peptic ulcer disease (Mózsik et al., 1965; 1967; 1969a; 1969b). These studied tried to reveal the details of absorption, metabolization and excretion of various anticholinergic agents in patients with peptic ulcer before the starting of chronic treatment, after the regular chronic treatment and after cessation of these drugs. The application of anticholinergic agents to patients was used to approach the cholinergic mediated processes both in the development and treatment of peptic ulcer diseases.

After the years of 1970, the H_2R blocking compounds became deeply studied in human GI physiology, pathology and pharmacology. Many clinical pharmacological studies with H_2R blockers have been carried out in patients with peptic ulcer disease (Mózsik et al., 1994; Patty et al., 1984; Tárnok et al., 1979; 1983). In the last two decades the proton pump inhibitors were deeply studied.

The problems, results and difficulties of our clinical pharmacology practice put down the bases of a very clear research line for the observations of capsaicin. The results of the different animal

observations offered a new possibility for evaluation of capsaicin sensitive afferent nerves (by the application of capsaicin) during physiological, pathological, pharmacological and therapeutic events of the GI tract (Mózsik et al., 2014).

The results from animal experiments with capsaicin which is widely used in the every-day culinary practice, clearly indicated us that the stimulatory doses of capsaicin acting on capsaicin-sensitive fibres produce gastric mucosal defensive actions and they are able to prevent the NSAID-induced gastric mucosal damage. These scientifically carried out studies with capsaicin in animals also offered a new tool to approach the capsaicin sensitive afferent nerves in the healthy human beings, and to some extent in patients with different GI disorders.

Our studies with capsaicin in human healthy subjects and in patients with different gastrointestinal disorders have been stated from 1997. These studies were permitted by the Regional Ethical Committee of University of Pécs, Hungary, and these observations were carried out according to Good Clinical Practice respecting the Helsinki Declaration.

The human observations were carried out according to the basic laws of human clinical pharmacology (inclusion and exclusion criteria, randomization, prospective studies, generally self-controlled group of healthy human subjects, etc).

We had five aims in these studies with the capsaicin:

1. To understand the main mechanisms of capsaicin sensitive afferent nerves in the gastric functions;
2. To try to understand the potential role(s) of capsaicin sensitive afferent nerves in the development of human physiological, pathological and pharmacological events;
3. To identify the dose range of capsaicin which stimulates only the capsaicin-sensitive afferent nerves and to identify the classical molecular pharmacological parameters (affinity and intrinsic activity curves, ED_{50} and pA_2 values) in comparison the same parameters obtained in cases of every day used drugs;
4. To exclude clearly the existence of desensitation of capsaicin-sensitive afferent nerves to capsaicin (under different observation circumstances, namely in acute administration, before and after two weeks capsaicin treatment, given in dose of 3 x 400 μg /day) to capsaicin;
5. To process and even to produce a new capsaicin containing drug or drug combinations to modify the capsaicin-sensitive afferentation in human healthy subjects and to treat patients with GI mucosal damage against NSAIDs and H. pylori infection.

These aims determined us to use a significant number of the methodologies applied in the human studies. However, we had to use classical molecular pharmacological methods to compare and to understand some details of capsaicin-induced changes in the human physiological, pathological parameters.

The following main trends were applied in the capsaicin research:

1. To determine the dose-response curves for the various drugs and capsaicin.

2. To introduce the classical molecular pharmacological methods for understanding the capsaicin-induced action in comparison to others produced by anticholinergic drugs, H_2R antagonists or proton pump inhibitors.

3. The specific immunohistochemistry (for obtained morphological evidence) was incorporated into the research.

4. Different parameters were simultaneously measured (e.g. plasma glucose, insulin, C-peptide and glucagon were detected during the sugar loading test in the healthy human subjects).

5. Capsaicin studies were carried out not only in acute administration and after a chronic capsaicin administration.

6. The immunohistochemical studies were carried out in the GI mucosa of patients with different GI disorders (acute gastric mucosal damage, chronic inflammation, precancerous state and cancers in the stomach and in the large bowel);

7. The human pathological diagnosis was given by an independent pathologist.

8. The ED_{5O} (necessary doses of drugs to produce 50% inhibition) values were determined and expressed in [-] molar values (pD_2).

9. To evaluate the possible role of capsaicin afferentation in the prevention or treatment of gastric mucosal damage produced by NSAIDs in healthy subjects and in patients who are treated with these drugs (as pain killers, platelet aggregation, anti-inflammatory compounds, etc).

4.1. Capsaicin-sensitive efferent nerves vs. gastric secretion in healthy human subjects

The capsaicin dose-dependent manner decreased the gastric basal secretion (BAO) (Mózsik et al., 1999; 2004a; 2005). The capsaicin was applied in very small doses (200 to 800 μg orally), which stimulate the capsaicin-sensitive afferent nerves.

When we applied the molecular pharmacological approach the actions of capsaicin, anticholinergic agents, H_2R antagonists or proton pump inhibitors, we were surprised that capsaicin was able to inhibit gastric acid secretion in smaller molar concentration than other clinically widely used drugs (Figures 3 and 4). Analyzing the intrinsic activity of these drugs and capsaicin by the molecular pharmacological methods (intrinsic activity of atropine was taken to be 1.00), we found capsaicin's action to be lesser than atropine's (Figure 3).

The affinity curves of different drugs and capsaicin were molecular pharmacologically determined and given as pD_2 (the necessary doses of drugs and capsaicin to produce 50% inhibition of gastric acid secretion (basal acid output), which expressed in [-] molar value) and as intrinsic activity (pA_2) (the necessary doses of drugs and capsaicin to produce 50% inhibition, also expressed in [-] molar) values (Table 1).

The results of these molecular pharmacological studies clearly indicated the sensitivity of the various regulatory targets of different drugs and capsaicin in comparison to possible physio-

logical roles of the target organs and the drug actions influence their functional activities and states. There is no question that the stimulation of capsaicin-induced afferent sensitive nerves plays a very significant effect in regulatory processes important for the maintenance of gastric mucosal integrity in human beings (including in healthy subjects and patients with different GI disorders or treated with different drugs, especially with NSAIDs).

The decrease of gastric acid secretion was explained by the increased H^+back diffusion after capsaicin application via the increased vasodilatator processes induced by the release of the CGRP and SP in animal observations or by the increase of somatostatin secretion. The CGRP and SP together with capsaicin receptor (TRVP1) can be detected by inmunohistological methods in the gastric mucosa around nerves, vascular spaces, parietal cells and in epithelial layer.

The increased gastric secretory responses are present along with increased gastric mucosal blood flow. On the other hand, the increased gastric acid (H^+) secretion is closely associated with the increase of K^+, Mg^{2+}, $Ca^+$and albumin in gastric juice. However, the decrease of gastric acid secretion produced by antisecretory agents is associated with the decrease of H^+, K^+, Mg^{2+}, $Ca^{2+}$and albumin (Myren, 1968).

Human observations with capsaicin do suggest presence of increased H^+back diffusion during capsaicin action (except when capsaicin was given in high doses):

1. The increased H^+back diffusion suggests the decreased level of albumin in the gastric juice. Our results cannot prove the existence of gastric H^+back diffusion in human healthy subjects during the capsaicin action:

2. We calculated the "parietal" and "non-parietal "components of gastric juice after Hollander's original observation (Hollander 1934). Our results clearly indicate that the decrease of gastric H^+concentration (and output) is closely associated with the increased extent of "non-parietal component" during the capsaicin action in the healthy human subjects. The "non-parietal component" of the gastric juice is a buffering part, which cannot be obtained in circumstance of passive metabolic processes. Earlier, the significant increase of buffering ("non-parietal component") secretion was obtained in 2-10 days after cessation of a prolonged atropine treatment in patients with peptic ulcer disease (Antal et al., 1966).

3. There are other arguments also exist against the existence of the passive H^+back diffusion in the stomach during capsaicin action in the healthy human subjects. When the capsaicin was directly given to gastric mucosa (using gastroscope), then GTPD increased in a dose dependent manner (Mózsik et al., 2005).

If ethanol was intragastrically given (using the biopsy channel), then GTPD immediately decreased, which could be reversed by the topical application of capsaicin. This action is also dose-dependent from capsaicin after ethanol application in the healthy human subjects (Mózsik et al., 2005).

The capsaicin action on the gastric secretory responses can be explained by different ways:

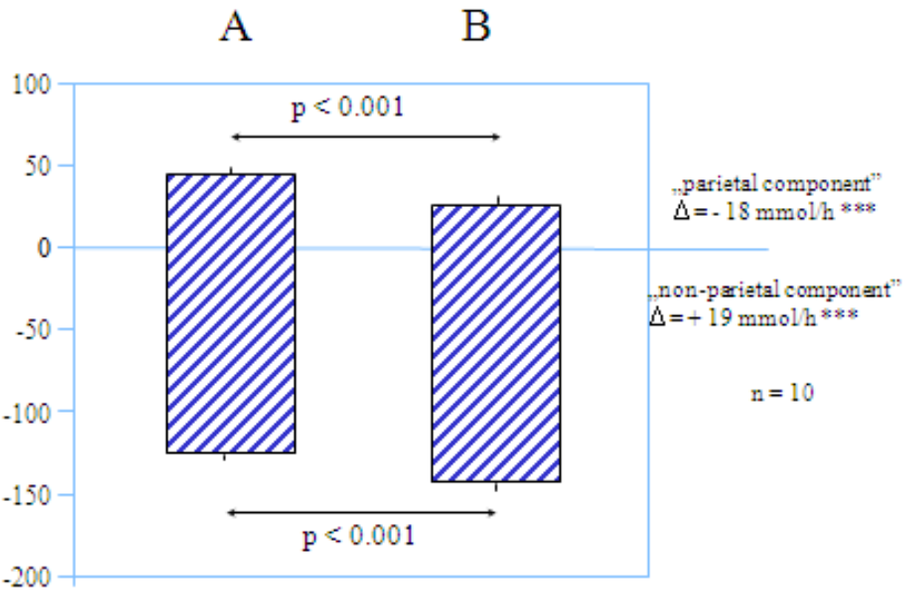

Figure 22. Changes of parietal and non-parietal components of gastric juice before (A) and after (B) capsaicin (400 μg orally, ED_{50} value) administration.

CAPSAICIN-INDUCED CHANGES IN THE "PARIETAL" AND "NON-PARIETAL" COMPONENTS OF GASTRIC JUICE

without capsaicin

	H^+	K^+	Na^+	Ca^{2+}	Mg^{2+}	$chloride^-$ proteins (albumin)
$H^+\uparrow$	↑	↑	↓	↑	↑	↑ ↑
$H^+\downarrow$	↓	↓	↑	↓	↓	↓ ↓

after capsaicin treatment (ED_{50})

↓	↓	↑	↓	↓	unchanged increased
Typical changes to decrease of inhibition of BAO in human healthy subjects					CAPSAICIN-INDUCED CHANGES

Figure 23. Changes in the contents of electrolytes of gastric juice with increase and decrease of H^+output, without (upper part) and with (below part) capsaicin application.

1. direct cellular action of capsaicin on the parietal cells;
2. direct stimulatory action of capsaicin on the "non-parietal component" of gastric secretory responses;

3. the capsaicin (given in doses producing the stimulation of capsaicin-sensitive afferent nerves) results directly neural (or hormonal) influences on the gastric mucosa;

4. other yet not known mechanism(s) existing in the regulation of the human gastric secretion.

The capsaicin given in ED_{50} increased the gastric emptying (Debreceni et al, 1999; Mózsik et al., 2004a, 2004b). This action of capsaicin on the gastric emptying can be explained at least by two pathways:

1. decrease of gastric acid secretion;

2. direct action on muscular function of the stomach (pylorus).

Up to now, the acute action of capsaicin was evaluated dominantly by the measuring one or two parameters.

4.2. Capsaicin action of glucose absorption from small intestine in human healthy subjects and its hormonal and metabolic backgrounds

The sugar loading test was applied for measuring absolutely different physiological events, e.g. glucose absorption from the proximal part of the small intestine and consequently the produced hormonal regulations during the glucose loading test.

The response to glucose loading in healthy human subject can be divided into three different periods on basis of physiological events after orally applied glucose in human healthy persons:

1. absorption (first period, from 30 to 90 min);

2. insulin (and other hormones) release (second period, from 60 to 150 min);

3. glycogen mobilization by the liver (third period, from 150 to 180 min) under adrenergic neural influences.

The glucose can be absorbed from the proximal part of the small intestine by active transport mechanism (in presence of Mg^{2+}, mitochondrial ATP breakdown into ADP) (Dömötör et al., 2006b). The monitoring of the glucose level was used as biological marker for the equilibrium of the different physiological events. In the first period the plasma glucose level depends only on the glucose absorption; in the second period the plasma level of glucose represents the equilibrium between the absorption and hormone release; and in the third the glucose level represents the mobilization of glucose by the liver in healthy human subjects. It is also important that the insulin and glucagon act contra regulatory on glucose utilization in the serum.

By studying the time sequence of changes in plasma levels of glucose, insulin, C-peptide and glucagon after glucose loading in healthy human subjects without and with capsaicin (400 μg orally), we found the followings:

1. The plasma level of glucose (from 30 to 150 min) and the glucagon (from 90 to 180 min) increased significantly after glucose plus capsaicin administration.

2. The plasma levels of insulin and C-peptide were increased from 90 to 165 min, however, no significant changes were observed between subjects without and with capsaicin.

3. No significance in timing of insulin and glucagon release was observed, which clearly excludes the existence of antagonism between insulin and glucagon release (short time).

4. The plasma level of glucagon was high for longer period than it was in case of insulin. It should be noted that capsaicin increased the glucagon level.

The results clearly indicate that capsaicin sensitive afferent nerves have a key-role in the regulation of glucose absorption from the small intestine (due to a local increase of blood flow), glucose utilization, and release of neuropeptide (presently the glucagon release). This human observation proved clear-cut the active participation of capsaicin sensitive afferent nerves in the carbohydrate metabolism (by the ways of modification of sugar absorption, hormone release). Up till now only the somatostatin release induced by capsaicin has been known (Szolcsányi, 2004).

4.3. Capsaicin given orally in small doses prevents with IND-induced gastric microbleedings in human healthy subjects

The IND was used in these studies as NSAID, which is a non-selective COX blocker (the ratio of ED_{50} of IND on COX-1 /COX-2 = 0.30) (Kawai et al., 1998) (Table 5). The extent of gastric microbleeding appears as consequence of COX-1 and COX-2 inhibition.

The results of our observations (Sarlós et al., 2003; Mózsik et al., 2003, 2004a; 2005) the capsaicin (ig. given) dose dependently prevented the IND-induced gastric microbleeding before and after 2 weeks capsaicin treatment.

Under the results of Kawai et al. (1998), we calculated the extents of gastric microbleeding depending on COX-1 and COX-2 enzyme activity (Table 6). It was found that the capsaicin-induced gastric mucosal protection remained unchanged – before and after 2 weeks capsaicin treatment – after both COX-1 and COX-2 enzyme inhibition.

NSAID	Ratio COX-1 : COX-2
Aspirin	0.12
Diclofenac	38.00
Etodolac	179.00
Ibuprofen	0.86
Indomethacin	**0.30**
Loxoprofen-SRS	3.20
NS-398	1263.00
Oxaprozin	0.061
Zaltoprofen	3.80

Table 5. Comparison of inhibitory effects (IC_{50}) of NSAIDs on COX-1 and COX-2 enzymes in human platelet synovial cell (After Kawai et al.: Eur. J. Pharmacol. 347; 87-94, 1998).*

- **IC_{50} VALUE OF INDOMETHACIN TO RATIO OF COX-1/COX-2 = 0,30 (1: 3,25)**
- **MICROBLEEDING IN THE STOMACH**

← 2 weeks capsaicin treatment →		
	Before	**After**
Baseline	**2,1 ± 0,1 mL/day**	**2,0 ± 0,1 mL/day**
After IND	**8,25 ± 0,25 mL/day**	**7,8 ± 0,3 mL/day**
Δ IND-induced	**6,15 ± 0,2 mL/day**	**5,8 ± 0,3 mL/day**
	(= inhibition on COX-1 + COX-2) (= 100%)	
COX-1:	**1.447±0.1 mL/day**	**1.364±0.1 mL/day**
COX-2:	**4.70±0.2 mL/day**	**4.44±0.2 mL/day**

- **400 μg CAPSAICIN (IG GIVEN) INDUCED DECREASE OF IND-GASTRIC MICROBLEEDING**

6±0.2 mL/day	**5.9±0.2 mL/day**

* means±SEM in 14 human healthy subjects.

Table 6. Correlation between the capsaicin actions, COX-1 and COX-2 systems and gastric microbleedings produced by indomethacin (IND) in human healthy subjects before and after 2-week capsaicin (3x400μg orally) treatment. (After Mózsik et al.: Inflammmopharmacology 15: 232-45, 2007)*

The orally given 200, 400 and 800 μg capsaicin dose dependently reduced the IND-induced gastric microbleeding. All of the healthy persons included in this study received all the mentioned doses of capsaicin in random allocation.

4.5. Questions of desensibilization in capsaicin receptor to capsaicin

4.5.1. Facts to exclude the presence of the desensibilization of capsaicin receptor to applied doses of capsaicin in acute observation circumstances

When we applied the capsaicin twice in doses of 800 μg ig. after 5 min interval, then we received the same extents of increase in difference of GTPD, indicating a very active metabolic action under these observation circumstances.

The same extent gastric mucosal protection was obtained in the IND-induced gastric mucosal damage in human healthy subjects. The actions of gastric mucosal prevention was dose-dependent on the IND-induced gastric microbleedings (please note that these human observations were carried out in prospective, randomized and multiclinical studies) (Figures 18 and 19).

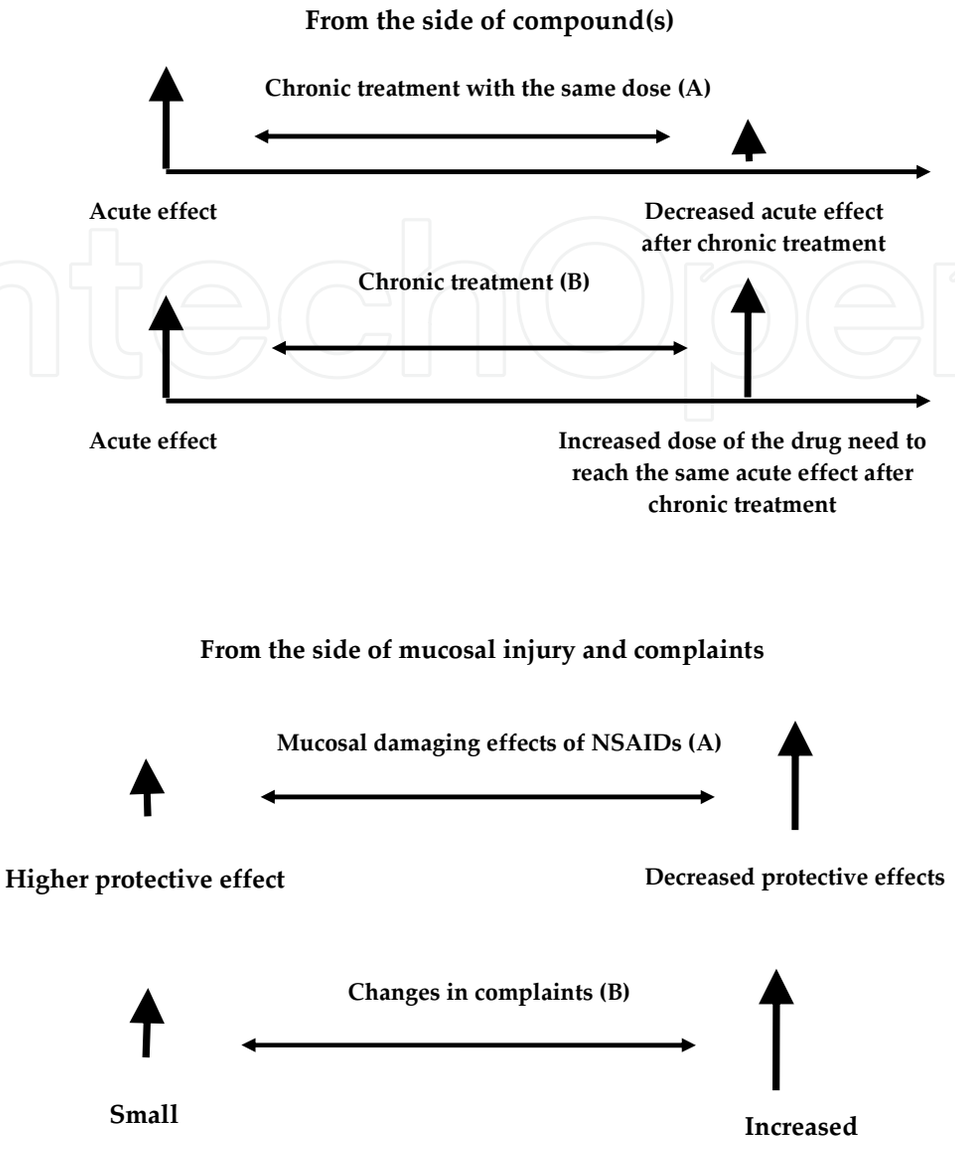

Figure 24. Schematic demonstration the possible pathways in changes of chronic capsaicin treatment from the side of the compound (upper part) and from the side of mucosal injury and complaints (lower part) in human healthy subjects and in patients with different (including gastrointestinal) disorders.

The results of these mentioned observations clearly indicated that the doses of capsaicin in our studies could not produce desensibilization of capsaicin receptors (these doses of capsaicin only were able to stimulate the capsaicin-sensitive afferent nerve).

4.5.2. Facts to exclude the presence of desensibilization to capsaicin receptor by applied doses of capsaicin during 2 weeks capsaicin treatments

The capsaicin exerts gastroprotective effect remained unchanged on IND-induced gastric mucosal microbleeding before and after 2-week capsaicin (3x 400μg orally given) treatment (Figures 19 and 24.

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By other words, the gastric baseline microbleeding remained unchanged after the application of different doses of capsaicin (200, 400 and 800 μg orally) induced gastric mucosal prevention.

The registration of these facts are very important, since a very wide scale of capsaicin doses applied in human observations resulted very contradictory data (capsaicin were applied in stimulatory doses to capsaicin sensitive afferent nerve and much higher doses producing reversible and irreversible inhibitory actions in various animal experiments).

The capsaicin acts at the level of capsaicin receptor, which has been cloned (Caterina et al., 1997). It is true that the capsaicin action depends on its doses proved by animal experiments (Szolcsányi, 1984; Mózsik et al., 2001). The small dose (400 μg=ED_{50}) was applied for two weeks (in dose of 400 μg x 3 orally) in healthy subjects. The gastric mucosal microbleeding was produced by orally given IND (Figure 19 and Table 6.

The following results were obtained:

1. The extent of baseline gastric microbleeding before and after 2 weeks capsaicin (without application of any drug) remained unchanged.
2. The extent of acutely given IND-induced gastric microbleeding was also unchanged.
3. The extent of capsaicin-induced gastric mucosal protection was also found to be the same (and dose dependent) before and after 2 weeks capsaicin treatment.

It has been concluded from these observations that the sensitivity of capsaicin receptor (TRVP1) unchanged, and on the other hand, the orally applied capsaicin is capable to exert gastric mucosal protection against IND.

Probably the applied small dose of capsaicin – used in our present studies – could not modify the TRVP1 receptor sensitivity. We have no knowledge in this field by using higher dose(s) of capsaicin in human healthy subjects.

These facts are very important from the point of selection of capsaicin containing drug, because these dosages of capsaicin could exert beneficial effect (given orally in small doses), meanwhile the capsaicin can produce reversible or irreversible damage on the human gastric mucosa.

Earlier similar types of observations were carried out with atropine and other parasympatholytics (Mózsik et al., 1965; 1967; 1969 a,b) and cimetidine (Wildersmith et al., 1990). Tolerance developed to the drugs applied chronically in patients with peptic ulcer disease, and the "pharmacological denervation hypersensibility" occurred with a clinically detectable tolerance (Mózsik et al., 1966; 1967; 1969). These clinical pharmacological examinations modified the periodicity and dosage of applicable drugs (used in chronic treatment).

The careful analysis of the results with capsaicin actions, COX-1 and COX-2 systems and gastric microbleedings produced by IND in human healthy subjects before and after two weeks capsaicin (3 x 400 μg orally) treatment offered an excellent possibility to approach the capsaicin actions on the COX-1 and COX-2 enzyme system (Table 6).

4.5.3. Gastric (gastrointestinal) cytoprotection vs. capsaicin actions (given in stimulatory doses of capsaicin-sensitive afferent nerves)

Observations with different chemical agents (drugs, mediators, nutritive agents like retinoids, prostaglandins and others) indicated a special gastric mucosal protection, which did not depend on the gastric acid inhibition (see the reviews Mózsik et al. 2010, 2011). Later on, many observations indicated that the so-called gastric cytoprotective agents are able to prevent the development of injuries of numerous organs (produced by different actions) and they can accelerate healing processes.

The existence of gastric cytoprotection was earlier proved in patients with peptic ulcer (Mózsik et al., 1965, 2010, 2011) as it was nominated by André Robert (1979).

Only few points are interesting in our present position, namely: 1. the capsaicin-induced gastric mucosal protection in human healthy subjects is accompanied by the decrease of gastric acid secretion (that was one of the criteria differed from "classic" gastric cytoprotection); 2.both "classical cytopotective effects" as well as capsaicin-produced gastric mucosal protection disappear after surgical vagotomy (but not after chemical vagotomy); 3. gastric cytoprotective effect produced by different agents remained to be the same besides application of capsaicin (given in doses to produce stimulation of capsaicin-sensitive afferent nerves) (Mózsik et al., 1997). These results offer us to suggest that: 1. some part a gastric mucosal (cyto)protection is very closely associated with the functional activity of capsaicin-sensitive afferent nerves; 2. increased extent of gastric mucosal damage might develop in consequence of surgical ablation of capsaicin-sensitive afferent nerves (Mózsik et al., 1982, 2011).

These lines of capsaicin and cytoprotection protection in some meaning are similar and differ from each other (Szabó et al., 2012; Mózsik et al., 2011).

4.5.4. Distribution of capsaicin receptor, CGRP and SP in the gastric and large bowel mucosa of patients with different gastrointestinal disorders

The use of specific antisera against TRVP1 receptor, CGRP and SP released by the stimulation of capsaicin sensitive afferent nerve can immunohistochemical demonstrate their presence in the GI mucosa. Please note, that mucosal biopsy cannot be performed in healthy human subjects due to ethical regulations. So „healthy subjects"are represented by human subjects with functional disorders having no endoscopic abnormalities and diagnosed by clinicians and independent pathologist. There is another problem, namely the regular biopsy can be offered a small tissue sample for its regular pathological histological evaluation. Our specific immunohistochemical observations could be done only after successful routine histological examination.

We studied l78 patients with different gastrointestinal disorders (complaints), and the persons, who had normal histology based on the opinion of independent pathologist, were used as normal (healthy) human subjects (Dömötör et al., 2007; Mózsik et al., 2007).

The TRVP1 receptor, CGRP and SP neuropeptides released by the stimulation of capsaicin receptor can be shown by immonohistochemistry both in the human gastric and colon mucosa.

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The TRVP1 receptors and neuropetides (CGRP and SP) could be demonstrated in the GI mucosa around the nerve endings, vascular elements, parietal cells, and also in epithelial layer.

The capsaicin application and the immunohistochemical demonstration of TRVP1 receptor in the GI tract newly met in the healthy human subjects. We studied the immunohistochemical distribution of TRVP1, CGRP and SP in the GI mucosa of patients with different disorders. The TRVP1 receptor, CGRP and SP could be detected practically in all patients with different acute, chronic diseases (including benignant, precancerous and cancerous diseases) (Dömötör et al., 2005). The results of these observations can be taken only as preliminary results. Their expression differed significantly in the GI mucosa of patients with acute and chronic disorders. Of course, the critical evaluation of these immunohistochemical observations is extremely hard, since we have only very limited information on the origin, stages, time periods of diseases, drug therapies and suggested etiological backgrounds. The studies dealing with the changes of individual patients with chronic GI disorders – in this research respect – are in progress. We have to emphasize two different main points in these studies, namely 1. The changes of the expressions of TRVP1, CGRP and SP are helpful from the point of development of GI mucosal injury and prevention, and 2. probably the participations of TRVP1, CGRP and SP differ in these GI pathological circumstances.

4.6. Immunohistochemical examinations in patients with chronic H. pylori positive and negative gastritis

In model human observations, the possible participation of TRVP1, CGRP and SP were studies in patients with chronic gastritis. The laboratory tests (quick urease test, urea breath test) and specific histological staining widely used in every day medical practice for demonstration of the presence of H. pylori infection were used, which suggested the presence of bacteria as the etiological for chronic gastritis.

Our studies were carried out in patients with H. pylori positive and negative chronic gastritis. The expression of TRVP1, CGRP and SP increased significantly in the gastric mucosa with chronic gastritis; however, no difference was obtained their expression in patients with H. pylori positive and negative chronic gastritis (Dömötör et al., 2006a).

The inflammation of the tissues does not represent a specific tissue reaction to inducing agents. This statement can be concluded from our results obtained in patients with H. pylori positive and negative chronic gastritis due the potential role of capsaicin sensitive afferent nerves. There is no question that the so-called „neurogenic inflammation" participated in the „general inflammatory processes" in patients with different gastrointestinal disorders.

4.7. Capsaicin sensitive afferentation in patients with chronic H. pylori positive gastritis before and after eradication treatment

The last step of our observations indicated that capsaicin-sensitive afferentation did not differ before and 6 weeks after successful eradication treatment in patients with chronic H. pylori positive gastritis (meanwhile the control biopsy was normal in 22 %, in 78% of cases it indicated

a moderate improvement of the histological picture of gastritis) (Lakner et al, 2011; Mózsik et al., 2011, Mózsik et al., 2013; Czimmer et al., 2013).

After careful analysis of these results, it can be stated that the capsaicin-sensitive afferentation represents as an essential pathway in the healing of chronic gastritis (probably without and with H. pylori infection). These results suggest an independent mechanism in the healing of chronic gastritis which differs from the eradication treatment. By other words, besides the H. pylori infection other factors might exist. The H. pylori infection can be taken as one (but probably most important) exogenous factor, however, the capsaicin-sensitive afferent fibres of vagal nerve represents an endogenous factor in the injury and protection of gastric mucosa (Mózsik et al., 2013).

Our results with capsaicin (in healthy human subjects and in patients with different gastrointestinal disorders) are summarized in Figure 21. The vagal nerve is able to modify the GI tract by regulatory steps at the central nervous system and at the level of target organ. The peripheral action of capsaicin is a dose dependent action (Szolcsányi, 1984; Mózsik et al., 2001) (Table 5). The capsaicin mobilizes the CGRP and SP (Inui et al., 1991; Dömötör et., 2005), which modifies the vascular reactions in the GI mucosa (Sipos et al. 2006), recently demonstrated that the existence of neuroimmune link between the CGRP, SP and immune cells in the gastric mucosa of patients with chronic gastritis. Dömötör et al. (2006b) demonstrated the increased release of glucagon during a sugar loading test in healthy human subjects, indicated a new step of capsaicin-induced changes taking place between the capsaicin sensitive afferent nerves and neurohormonal regulation. Dömötör et al. (2006b) gave a direct evidence for the role of capsaicin in the carbohydrates metabolism.

There were a few very surprising matters due to capsaicin from the point of human classical clinical pharmacology prior our observations:

1. no permitted orally applicable capsaicin preparation was available for humans;
2. no chronic toxicology was known to capsaicin by animal observations;
3. no direct clinical pharmacological study had been performed to determine germinative function;
4. the capsaicin (Sigma-Aldrich, USA) chemically is not uniform due to its varying content of dihydrocapsaicin, nordihydrocapsaicin and some other capsaicinoids;
5. no classical human clinical pharmacological study (human phase I and phase II) was found in the literature;
6. no correct Drug Master File (DMF) for capsaicin preparation were developed for the commercially obtained capsaicin (exception of a certain capsaicin preparation obtained from India and used by us);
7. no human pharmacokinetic observations were available for capsaicin (please remember that our capsaicin studies in human healthy subjects were started in 1997).

Bernard et al. (2008) were unable to create pharmacokinetic profile of capsaicinoids after administration of 15 and 30 mg of capsaicin/person; meanwhile, the detection limit was 10 ng/

ml. Chaiyasit et al. (2009) after the application of 5 gram of C. frurenscens orally (equivalent to 26.6 mg pure capsaicin) found that the capsaicin could be detected in plasma after 10 min, and the peak concentration (C_{max}) was 2.47 ± 0.13 ng/mL, t_{max} was 47.1 ± 2.0 min and $t_{½}$ was 24.9 ± 5.0 min. After 90 min, capsaicin could not be detected in the plasma. Chaiyasit et al. (2009) explained the results of Bernard et al. (2008) by the time factor of pharmacokinetic behaviors of capsaicin in humans. The results of these observations were mentioned in the review paper by O'Neill et al. (2012).

We also received new information from the chronic toxicological studies in Beagle dogs (2008). These animals were treated with different doses (0.1, 0.3 and 0.9 mg/kg body weight/day orally given) of capsaicin(noids) for one month. No toxic effects were observed in these dogs during the whole treatment periods. We noticed surprisingly that capsaicin and dihydocapsaicin could not be detected in the sera of Beagle dogs by either high pressure chromatography with the detection limit of 20 ng/mL serum or liquid chromatography-mass spectrometry with the detectation was 26 fg/mL in the serum at any time after the oral administration (Mózsik et al., 2008; Boros et al., 2008).

5. Main conclusion from our obervations on capsaicin application in human healthy subjects and in patients with different disorders

1. The capsaicin (as a specific agent to stimulate the capsaicin-sensitive afferent nerves) plays a special role in the regulation the gastric functions (decrease of gastric acid secretion, increase of gastric emptying, increase in "buffering part" of the gastric secretion, increase of GTDP), absorption of glucose (and in its metabolism as well as in increase of glycagon release) in human healthy subjects, when it is applied in stimulatory doses;
2. The capsaicin given orally in stimulatory doses protects against the alcohol-and NSAID-induced gastric mucosal damage in healthy human subjects;.
3. If the capsaicin is given in stimulatory doses to capsaicin-sensitive afferent nerves in human healthy subjects, it will not produce desensibilization of its receptor (neither in acute administrations nor in chronic administrations) in human healthy subjects ;
4. The presence of capsaicin receptor (also CGRP and SP, which are very close in physiological relation) can be shown by specific immuno-histochemical methods under various GI disorders ;
5. The capsaicin-induced gastroprotection differs from the eradication treatment in patients with chronic H. pylori positive gastritis (and probably the roles of capsaicin receptor and CGRP differ from SP);
6. Very important to note that these gastroprotective actions can be obtained only by administration of capsaicin in stimulatory doses to its sensitive afferent nerves.

After looking of this conclusion list, there are clear evidences that the capsaicin is an orally applicable drug either alone or in combinations with different NSAIDs to human healthy

subjects and to patients. Its indication is wide from prevention against drug-induced gastric mucosal damage, from patients under long term aspirin treatment (due to cardiovascular disease, thrombophylia, rheumatoid arthritis), pain killer treatment, patients having chronic H. pylori positive gastritis and to patient with different carbohydrate disorders.

We are of the opinion that we scientifically put down the clinical pharmacological bases of the oral capsaicin or drug combination use. We are in need of competent pharmaceutical partners for commercial introduction of these drug candidates into the everyday medical treatment (Mózsik, 2014; Mózsik et al., 2014).

Of course, we are aware that many other observations are need to be carried out in according to the regulations of international drug development, production and marketing for a capsaicin containing drug to licensed for everyday medical treatment.

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The authors confirm that this overview content has no conflicts of interest.

References

[1] Abdel-Salam OME, Czimmer J, Debreceni A, Mózsik Gy (2001) Gastric mucosal integrity: Gastric mucosal blood flow and microcirculation. An overview. J Physiol Paris 95: 105-127

[2] Abdel-Salam OME, Debreceni A, Mózsik Gy (1999) Capsaicin-sensitive afferent sensory nerves in modulating gastric mucosal defense against noxious agents. J. Physiol Paris 93 : 443-454

[3] Aijoka H, Matsuura N, Miyake H (2002) High quality of ulcer healing in rats by lafutidine and new-type histamine H_2 receptor antagonist: involvement of capsaicin of sensitive sensory neurons. Inflammopharmacology 10: 483-493

[4] Aijoka H, Miyake H, Matsuura N (2000) Effect of FRG-8813, a new-type histamine H_2-receptor antagonist, on the recurrence of gastric ulcer healing by drug treatment. Pharmacology 61: 83-90

[5] Antal L, Mózsik Gy, Jávor T, Krausz M. (1965) The electrolyte content of gastric juice after prolonged atropine treatment. In: Magyar I (ed) Acta Tertii Conventus Medicinae Internae Hungarici. Gastroenterologia. Akadémiai Kiadó, Budapest, pp 167-169

[6] Bernard BK, Tsubuku S, Kayhara T, Maeda K, Hanada M, Nakamura T, Shirai Y, Nakayaha A, Ueno S, Mihara H (2008) Studies of the toxicological potential of capsaicinoids. X. Safety assessment and pharmacokinetics of capsaicinoids in healthy male vlonteers after single oral ingestion of CH-19 Sweet extract. Int J Toxicol 27 (Suppl 3): 137-147

[7] Boros B, Dornyei Á, Felinger A (2008) Determination of capsaicin and dihydrocapsaicin in dog plasma by Liquid Chromatography- Mass Spectography (analytical method report). PTE TTK Analitikai Kémiai Tanszék, Pécs,Hungary

[8] Buck SH, Burks TF (1986) The neuropharmacology of capsaicin: a review of some recent observation. Pharmacol Rev 38: 179-226

[9] Caterina MJ, Schumacher MA, Tominaga H, Rosen TA., Levine JD, Julius D (1997) The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature 389: 816-824.

[10] Chaiyasit E, Khovidhunkit W, Wittayertpanya S (2009) Pharmacokinetic and the effect of capsaicin in Capsicum flourescens on decreasing plasma glucose level. J Med Assoc Thai 92:108-113

[11] Czimmer J, Szabó IL, Szolcsányi J, Mózsik Gy (2013) Capsaicin-sensitive afferentation represents a new mucosal defensive neural pathway system in the gastric mucosa in patients with chronic gastritis.In: Mozsik Gy (ed) Current Topics in Gastritis – 2012.INTECH Publishers, Rijeka, Croatia, pp 61-75

[12] Csáky TZ (1969) Introduction to general pharmacology. Appleton–Century-Craft Educational Division, Meredith Corporation, New York. pp 17-34

[13] Debreceni A, Abdel-Salam OME, Figler M, Juricskay I, Szolcsányi J, Mózsik Gy (1999). Capsaicin increases gastric emptying rate in healthy human subjects measured by ^{13}C-labeled octanoid acid breath test. J Physiol Paris 93: 455-460

[14] Dömötör A, Peidl Zs, Vincze Á, Hunyady B, Szolcsányi J, Szekeres Gy, Mózsik Gy. (2005) Immunohistocemical distribution of vanilloid receptor, calcitonin- gene related peptide and substance P in gastrointestinal mucosa of patients with different gastrointestinal disorders. Inflammopharmacology 13: 161-177

[15] Dömötör A, Kereskay L, Szekeres Gy, Hunyady B, Szolcsányi J, Mózsik Gy (2006a) Participation of capsaicin sensitive afferent nerves in the gastric mucosa of patients with Helicobacter pylori-positive or –negative chronic gastritis. Dig Dis Sci 52:411-417

[16] Dömötör A, Szolcsányi J, Mózsik Gy (2006b) Capsaicin and glucose absortion and utilization in healthy human subjects. Eur J Pharmacol 534:280-283

[17] Fisher MA, Hunt JN (1976) A sensitive method for measuring haemoglobin in the gastric juice. Digestion 14:409-414

[18] Gabella G, Pease H (1973) Number of axons in the abdominal vagus of the rat. Brain Res 58: 465-469

[19] Grijalva CV, Novin D (1990) The role of hypothalamus and dorsal vagal complex in gastrointestinal function an pathophysiology. Ann N Y Acad Sci.. 597: 207-221

[20] Hollander F (1934) The component of gastric secretion. Am J Dig Dis Sci 1:319-329

[21] Holzer P (1998) Neural emergency system in the stomachs. Gastroenterology 114: 823-839

[22] Holzer P (1999) Capsaicin cellular targets. Mechanisms of action, as selectivity for thin sensory neurons, Phamacol Rev 43:143-201

[23] Holzer P (2013) Transient receptor potential (TRP) channels as drug targets for diseases of the gastrointestional system. Pharmacol & Ther 131: 142-170

[24] Hossenbocus A, Fitzpatrick P, Colin-Jones DG (1975) Measurement of gastric potential difference at endoscopy. Gut 14: 410-415

[25] Inui T, Kinoshita J, Yamahuchi A, Yamatani T, Chiba T (1991) Linkage between capsaicin-stimulated calcitonin gene-related peptide and somatostatin release in the rat stomach. Am J Physiol. 261: G770-774

[26] Jancsó N, Jancsó- Gábor A, Szolcsányi J (1967) Direct evidence for neurogenic inflammation and its prevention by denervation and by pretreatment with capsaicin. Brit J Pharmacol 31:138-151

[27] Jancsó N.,Jancsó- Gábor A, Szolcsányi J (1968) The role of sensory nerves endings in the neurogen inflammation induced in human skin and in the eye and paw of the rat. Brit J Pharmacol 33: 32-41

[28] Jancsó-Gábor A, Szolcsányi J, Jancsó N. (1970) Irreversible impairment of the irregulation induced by capsaicin and similar pungent substances in rat and guinea-pigs. J Physiol London 206: 495-507

[29] Karádi O, Mózsik Gy (2000) Surgical and Chemical Vagotomy on the Gastrointestinal Mucosal Defense. Akadémiai Kiadó, Budapest

[30] Kawai S, Nishida S, Kato M, Furumaya Y, Okamoto R, Koshino T, Mizushima Y (1998) Comparison of cyclooxygenase-1 and -2 inhibitory activities of various nonsteroidal anti-inflammatory drugs using human platelets and synovial cells. Eur J. Pharmacol 347:87-94

[31] Lakner L, Dömötör A, Tóth Cs, Szabo IL, Mecker Á, Hajós R, Kereskay L, Szekeres Gy, Döbrönte Z, Mózsik Gy (2011) Capsaicin-sensitive afferentation represents an indifferent defensive pathway from eradication in patients with Helicobacter pylori positive gastritis. World J Gastrointest Pharmacol Ther 2: 36-41

[32] Marfertheimer P, Megraud F, 0'Morain C, Bazzoli F, El-Omar E, Graham D, Hunt R, Rokkas T, Vakil N, Kuipers EJ (2007) Current concept in the management of Helicobacter pylori infection: the Maastricht III Consensus Report. Gut 56: 772-781

[33] Mózsik Gy (2006) Molecular pharmacology and biochemistry of gastroduodenal mucosal damage and protection. In Mózsik Gy (ed) Discoveries in Gastroenterology: from Basic Research to Clinical Perspectives (1960-2005). Akadémiai Kiadó, Budapest, pp 139-224

[34] Mózsik Gy (2010) Gastric cytoprotection 30 years after its discovery by André Robert: a personal perspective. Inflammopharmacology 18: 209-221

[35] Mózsik Gy (2014). Capsaicin is new orally applicable gastroprotective and therapeutic drug alone or in combination in human healthy subjects and in patients. In: Abdel Salam OME (Ed) Capsaicin as an Therapeutic Molecule. Springer Verlag, Basel, pp. 209-258.

[36] Mózsik Gy, Abdel-Salam OME, Szolcsányi J (1997) Capsaicin-Sensitive Afferent Nerves in Gastric Mucosal Damage and Protection. Akadémiai Kiadó Budapest.

[37] Mózsik Gy, Belágyi J, Szolcsányi J, Pár G, Pár A, Rumi Gy, Rácz I (2004a) Capsaicin-sensitive afferent nerves and gastric mucosal protection on human healthy subjects. A critical overview, in: Takeuchi K, Mozsik Gy (eds) Mediators in Gastrointestinal Protection and Repair. Research Signpost, Kerala, India, pp 43-62

[38] Mózsik Gy, Debreceni A, Abdel-Salam OME, Szabó I, Figler M, Ludány A, Juricskay I, Szolcsányi J (1999) Small doses capsaicin given intragastrically inhibit gastric basal gastric secretion in healthy human subjects. J Physiol Paris 93:433-436.

[39] Mózsik Gy, Berstad A, Myren J, Setekleiv J (1969a) Absorption and urinary excretion oxyphencyclamin HCI in patients before and after a prolonged oxyphencyclimide treatment. Med Exp 19: 10-16

[40] Mózsik Gy, Dömötör A, Past T, Vas V, Perjési P, Kuzma M, Blazics Gy, Szolcsányi J (2009) Capsaicinoids: from the Plant Cultivation to the Production of the Human Medical Therapy. Akadémiai Kiadó, Budapest

[41] Mózsik Gy, Hunyady B, Garamszegi M, Németh A, Pakodi F, Vincze A. (1994) Dynamism of cytoprotective and antisecretory drugs in patients with unhealed gastric and duodenal ulcers. J Gastroenterol Hepatol 9: S88-92

[42] Mózsik Gy, Jávor T (1969b) Development of drug cross-tolerance in patients treated chronically with atropine. Eur J Pharmacol 6:169-174.

[43] Mózsik Gy, Jávor T, Dobi S (1965) Clinical-pharmaological analysis of long term parasympatholytic treatment. In: Magyar I (ed) Acta Tertii Conventus Medicinae Internae Hungarici. Gastroenterologia.Akadémiai Kiadó, Budapest, pp 709-715

[44] Mózsik Gy, Jávor T, Dobi S, Petrássy K, Szabó A. (1966) Development of "pharmacological denervation phenomenon" in patients treated with atropine. Eur J Pharmacol 1: 391-395

[45] Mózsik Gy, Moron F, Jávor T (1982) Cellular mechanisms of the development of gastric mucosal damage and of gastroprotection induced by prostacyclin in rats. A pharmacological study, Prostagland Leukot Med 9: 71-84

[46] Mózsik Gy, Past T, Abdel-Salam OME, Kuzma M, Perjési P (2009) Interdisciplinary review for correlation between the plant origin capsaicinoids , nonsteroidal antiinflammatory drugs, gastrointestinal mucosal damage and prevention in animals and human beings. Inflammopharmacology 17: 113-150

[47] Mózsik Gy, Past T, Dömötör A, Kuzma M, Perjési P (2010) Production of orally applicable new drug or drug combinations from natural origin capsaicinoids for human medical therapy. Curr Pharm Des 16, 1197-1208

[48] Mózsik Gy, Past T, habvon T, Keszthely Zs, Perjési P, Kuzma M, Sándor B, Szolcsányi J, Abdel-Salam OME, Szalai M.(2014) Capsaicin is a new gastrointestinal mucosal protecting drug candidate in humans – pharmaceutical development and production based on clinical pharmacology. In: Mózsik Gy, Abdel-Salam OME, Takeuchi K (Eds) Capsaicin-Sensitive Neural Afferentation and the Gastrointestinal Tract: from Bench to Bedside. INTECH Publishers, Rijeka (in press).

[49] Mózsik Gy, Pár A, Pár G, Juricskay I, Figler M, Szolcsányi J (2004a) Insight into the molecular pharmacology to drugs acting on the afferent and efferent fibres of vagal nerve in the gastric mucosal protection In:: Ulcer Research, Proceedings of the 11th International Conference, Sikirič P., Seiwerth P., Mózsik Gy., Arakawa T., Takeuchi K. (eds) Ulcer Research, Proceedings of the 11th International Conference. Monduzzi, Bologna, pp 163-168.

[50] Mózsik Gy, Sarlos P, Racz I, Szolcsányi J (2003). Evidence for the direct protective effect of capsaicin in human healthy subjects. Gastroenterology 124: Suppl 1, A-454

[51] Mózsik Gy, Past T, Perjési P, Szolcsányi J (2008) Determination of capsaicin and dihydrocapsaicin content of dog's plasma by HPLC-FLD method. In: Mózsik Gy., Past T, Pejési P., Szolcsány J: Original reports on toxicology of capsaicin.VII. 8-day oral tocicity study of test item capsaicin natural USP 37 in Beagle Dogs (Final report). LAB International research Centre Hungary Ltd. Veszprém,Hungary by the date of final repot 13 June 2008.Study Code: 07/496-100K, pp 1-35 text and 190 pages in Appendices (Appendix 2.11) pp 1-37

[52] Mózsik Gy, Rácz I, Szolcsányi J (2005) Gastroprotection induced by capsaicin in human healthy subjects. World J. Gastroenterol 11: 5180-5184

[53] Mózsik Gy, Szabo IL, Czimmer J (2011a) Approaches to gastrointestinal cytoprotection: from isolated cell, via animal experiments to healthy human subjects and patients witg different gastrointestinal disorders. Curr Pharm Des 17: 1556-72

[54] Mózsik Gy, Szabó IL,Dömötör A (2011b) Approach to role of capsaicin-sensitive afferent nerves in the development and healing in patients with chronic gastritis. In: Tonito P (ed) Gastritis and Gastric Cancer. New Insights in Gastroprotection,Diagnosis and Treatments. INTECH Publishers, Rijeka, Croatia, pp 25-46

[55] Mózsik Gy, Szabó I L, Czimmer J (2014) Vulnerable points of the Helicobacter pylori story – based on animal and human observations (1975-2012).In: Buzas Gy (ed) Helicobacter Pylori – a Worldwide Perspective 2013.Bentham Science Publishers, Oak Park, IL, USA, pp. 429-480.

[56] Mózsik Gy, Szolcsányi J, Dömötör A. (2007) Capsaicin research as a new tool to approach of the human gastrointestinal physiology, pathology and pharmacology. Inflammopharmacology 15: 232-45

[57] Mózsik Gy, Vincze Á, Szolcsányi J (2001) Four responses of capsaicin sensitive primary afferent neurons to capsaicin and its analog. Gastric acid secretion, gastric mucosal damage and protection. J. Gastroenterol. Hepatol. 16:193-197

[58] Myren J (1968) Gastric secretion following stimulation with histamine, histology and gastrin in man. In: Semb L, Myren J (eds) The Physiology of gastric Secretion. Universitetforlaget, Oslo, pp 413-428

[59] Nagy L, Mózsik Gy, Feledi É, Ruzsa Cs, Vezekényi Zs, Jávor T (1984) Gastric microbleeding measurements during one day treatment with indomethacin and indomethacin plus sodium salicylate (1:10) in patients. Acta Physiol. Hung 64: 373-377

[60] O'Neill J, Brock C, Olesen E, Andersen T, Nilsson M, Dickenson AH (2012) Unravelling the mystery of capsaicin: a tool to understand and treat pain. Pharmacol Rev 64: 939-97

[61] Onodera S, Shibata M, Tanaka M (1999) Gastroprotective mechanisms of lafutidine, a novel anti-ulcer drug with histamine H_2-receptor antagonist activity, Artneim. Forsch., Drug. Res. 49: 519-526

[62] Onodera, S., Shibata, M., Tanaka M (2002) Gastroprotective activity of FRG-8813, a novel histamine H_2-receptor antagonist, in rats. Jpn J Pharmacol 68: 161-173

[63] Patty I, Tárnok F, Simon L, Jávor T, Deák G, Benedek Sz, Kenéz P, Nagy L, Mózsik Gy (1984) A comporative dynamic study of the effectiveness of gastric cytoprotection by the vitamin A, De-Nol, sucralfate and ulcer healing by pirenzepine in patients with chronic gastric ulcer (A multi-clinical and randomized study). Acta Physiol Hung 64:379-384

[64] Robert A, Nemazis JE, Lancastter C, Hanchar A (1979) Cytoprotection by prostaglandins in rats. Prevention of gastric necrosis by alcohol, HCl, NaOH, hypertonic NaCl and thermal injury. Gastroenterology 77: 4433-443

[65] Sarlós P, Rumi Gy, Szolcsányi J, Mózsik Gy, Vincze Á (2003) Capsaicin prevents the indomethacin-induced gastric mucosal damage in human healthy subject. Gastroenterology 124: Suppl. 1, A-511

[66] Sipos G, Altdorfer K, Pongor É, Chen LP, Fehér E (2006) Neuroimmune link in the mucosa of chronic gastritis with Helicobacter pylori infection. Dig Dis Sci 51: 1810-1017

[67] Szabo IL, Czimmer J, Szolcsányi J, Mózsik Gy (2013). Molecular pharmacological approaches to effects of capsaicinoids and of classical antisecretory drugs on gastric basal acid secretion and on indomethacin-induced gastric mucosal damage in human healthy subjects (mini review). Curr Pharm Des 19: 84-89

[68] Szabo S, Taché Y, Tarnawski A (2012) The "Gastric Cytoprotection" concept of André Robert and the origins of a new series of international symposia. In: Filaretova LP, Takeuchi K (eds) Cell/ Tissue Injury and Cytoprotection/Organoprotection in the Gastrointestinal Tract. Front Gastrointest Res. Basel, Karger. Vol. 30, pp 1-23

[69] Szállasi A, Blumberg M (1999) Vanilloid (capsaicin) receptors and mechanisms. Pharmacol Rev 51:159-211

[70] Szolcsányi J (1984) Capsaicin sensitive chemoprotective neural system with dual sensory-afferent function. In: Chalh LA, Szolcsányi J, Lembeck F (eds) Antidromic Vasodilatation and Neurogenic Inflammation. Budapest, Akadémiai Kiadó, pp. 27-56

[71] Szolcsányi J (1997) A pharmacological approach to elucidation of the role of different nerve fibres and receptor endings inmediation of pain. J Physiol Paris 73: 251-259

[72] Szolcsányi J (2004) Forty years in capsaicin research for sensory pharmacology and physiology. Neuropeptide 38: 377-384.

[73] Szolcsány J.(2014) Discovery and mechanism of gastroprotective action of capsaicin. In: Mózsik Gy., Abdel-Salam OME, Takeuchi K (eds). Capsaicin Sensitive Neural Afferentation and the Gastrointestinal Tract: from Bench to Bedside. INTECH Publishers, Rijeka,Croatia (in pres).

[74] Szolcsányi J, Barthó L (1979) Capsaicin-sensitive innervation of the guinea-pig small intestine and its selective blockade by capsaicin. Naunyn-Schmidede-berg's Arch Pharmacol 305: 83-90

[75] Szolcsányi J, Barthó L (1981) Impaired defense mechanisms to peptic ulcer in the capsaicin-desensitized rat. In: Mózsik Gy, Hänninen O, Jávor T (eds) Advances in Physiological Sciences Vol.29, Gastrointestinal Defense Mechanisms.Pergamon Press, Oxford-Akadémiai Kiadó, Budapest, pp 39-51

[76] Takeuchi K (2006) Unique profile of Lafutidine: a novel histamine H_2-receptor antagonist: mucosal protection throughout GI mucosal mediated by capsaicin-sensitive afferent nerves. Acta Pharmacol. Sinica Suppl.pp 27-35

[77] Tárnok F, Deák G, Jávor T, Mózsik Gy, Nagy L, Patty I (1983) Effect of combination atropine and cyproheptadine and atropine+carbenoxolone in duodenal ulcer therapy. Int J Tiss React 5:315-321

[78] Tárnok F, Jávor T, Mózsik Gy, Nagy L, Patty I, Rumi Gy, Solt I (1979) A prospective multiclinical study comparing the effects of placebo, carbenoxolone, atropine cimetidine in patients with duodenal ulcer. Drugs Exp Clin Res 5 : 157-166

[79] Vincze A, Szekeres Gy, Király Á, Bódis B, Mózsik Gy (2004) The immunohistochemical distribution of capsaicin receptor, CGRP and SP in the human gastric mucosa in patients with different gastric disorders.In: Sikirič , Seiwert S, Mózsik Gy, Arakawa T, Takeuchi K (eds). Ulcer Research.Proceedings of 11th International Congress of Ulcer Resarch. Monduzzi, Bologna, pp 149-153

[80] Wildersmith, CH, Ernst T, Gennoni M, Zeyen B, Halter F, Merki HS (1990) Tolerance to H_2-receptor antagonist. Dig Dis Sci 35: 976-983

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