THE CAPSAICIN- AND HELICOBACTER STRAINS-INDUCED CELLULAR MECHANISMS OF THE GASTRIC MUCOSA IN ANIMALS AND HUMANS

Ph.D. thesis

András Debreceni, M.D.

Tutor:
Gyula Mózsik, M.D., Ph.D., Sc.D.

First Department of Medicine, Medical Faculty,
University of Pécs, Hungary

2001

Tiszteletlel:
Debreceni András

The effect of intragastric capsaicin on gastric acid secretion and gastric emptying in human

Introduction

Capsaicin (8-methyl-N-vanillyl-6-noneamide) is the pungent alkaloid of the fruits of the genus Capsicum, and has the unique feature to cause a short, initial stimulation, and then - by desensitisation - blockage of a subset of mammalian afferent neurons with Aδ and C fibres called capsaicin sensitive primary afferent sensory fibres (CSPASF). These fibers are present in the afferents of the vagal, trigeminal nerve, and found in the spinal afferents of dorsal root ganglia. They contain bioactive peptide neurotransmitters as calcitonin gene related peptide, tachykinins - substance P and neurokinin A -, which are released from the nerve terminals under stimulation, and cause different local vascular tissue reactions and motor functions in the skin, mucosal surfaces, heart, etc. Because of this unique feature of these fibres to parallely signal the sensory stimulus from the nerve ending to the central nervous system, and exert efferent function too, the term and concept of dual sensory-efferent function was introduced for them.

According to a number of animal studies CSPASF have wide range of important roles including vascular, secretory and motor functions in the gastrointestinal tract, among them the gastric acid secretion (GAS) and gastric motility (GM). Furthermore a protective role for CSPASF in the stomach against different noxious agents by affecting gastric musosal blood flow, mucus, bicarbonate and acid secretion was found. As for GAS, our laboratory group earlier found that small dose capsaicin and the capsaicin analogue resiniferatoxin dose-dependently decreased GAS in pylorus-ligated rats. The investigations of the effect of capsaicin on GM in animals revealed that CSPASF have role in enterogastric motoric reflexes.

Because of the beneficial effects of capsaicin, and because capsaicin is consumed by human beeings as ingredient of such spices as (red) paprika, chilli, the effect of capsaicin on the gastric physiological parameters in human is of particular interest. However - in spite of the animals - we know less about the pharmacological effect of small dose capsaicin on gastric parameters in human, even these results are controversial. GAS was either increased or decresed after intragastric application of capsaicin containing spices. Studies with muscle stripes isolated from the gut of operated patients showed contractility under capsaicin stimulation, however there is no data about muscle stripes of the human stomach. Ingestion of big amount of capsaicin containing spices resulted in either delayed or shortened gastric emptying in human.

Therefore in these studies we intended to measure the pharmacological effect of small dose intragastric capsaicin on GAS and GM in healthy humans.

Aims

Our aims were in these studies the followings:

1. To measure the effect of small dose (100-800 ug) intragastrically given capsaicin (in concentrations of 3.2-26 mM) on GAS in healthy human volunteers.

2. After obtaining the result that capsaicin has an inhibitory effect on GAS, we aimed to determine the dose which inhibits the GAS by 50% (ID_{50}) for capsaicin on GAS.

3. Then we planned to identify the time for action of capsaicin on GAS.

4. We aimed to measure the gastric emptying rate after intragastric application of capsaicin in the same dose and concentration which was found to be ID_{50} on GAS.

5. We aimed to measure glucose absorption, insulin, C-peptide and glucagon hormon levels after application of the same dose and concentration of capsaicin as ID_{50} on GAS.

Materials and methods

The observations were carried out on healthy volunteers.

Gastric secretory measurements

The appropriate amount (100-800 ug) capsaicin was applied intragastrically in 100 ml physiological saline through a nasogastric tube.
The observations were performed according to two protocols to determine the effect of different doses of capsaicin on basal acid output, and the time for inhibitory action of capsaicin on GAS respectively.

Volume (in ml) of the suctioned gastric content was measured, and the volume of secreted gastric acid in the gastric content was determined by titration. Gastric acid output (in mmol/h) was calculated.

Gastric emptying measurements

100 mg ^{14}C-octanoic acid and 75 g glucose in 100 ml physiological saline was used for the gastric emptying measurements, which were performed with an Infra Red ISotope (IRIS) analyser on two consecutive days without and with 400 ug capsaicin respectively. Venous blood sample was obtained from the volunteers at the same time intervals as the exhalations were done.

Blood glucose level (in mmol/l) was determined enzymatically, and serum levels of insulin (ulU/ml), C-peptide and glucagon (pg/ml) were measured with ^{125}I-labeled radio immuno assay kits.

Results

Gastric secretory measurements

Gastric basal acid output was dose-dependently inhibited after intragastric application of 100-800 ug capsaicin.
The maximal, 800 ug capsaicin caused inhibition of GAS was regarded as 100%. Then the ID_{50}, the dose which inhibited GAS by 50% was found to be 400 ug.
The time-course curve obtained during the application of intragastric capsaicin in the dose of ID_{50} indicated 1 hour time for inhibitory action of capsaicin on GAS.

Gastric emptying measurements

After completing the infra-red spectroscopy measurements the IRIS machine created a gastric emptying curve for each investigation. After analysing four parameters of these curves obtained without and with application of 400 ug capsaicin intragastrically, we found that gastric emptying was significantly shortened in the capsaicin-treated cases.

Blood glucose and hormone levels

We represented the blood glucose and hormones levels against the time on a graph. When we analysed these concentration-time curves we found that there was no significant difference between the average glucose levels obtained without and with application of capsaicin. Although we found a slight increase regarding the

maximum glucose level in the capsaicin-treated group, this did not reach the level of significance. As for the hormones, the maximum and average levels of glucagone, but not insulin and C-peptide increased significantly during capsaicin application.

Discussion and conclusion

In these studies we found that intragastric capsaicin inhibits GAS, and increases gastric emptying rate in healthy humans. Present data strengthens the idea that capsaicin, the pungent alcaloid of spices exerts pharmacological effect in the human stomach, i.e. CSPASF have role in the gastric physiology in the human too. These effects of capsaicin may contribute to the protective effects of this agent and capsaicin containing spices found in animals and observed in humans. The decrease of acid produced in the stomach, and the shortened time for acid to cause gastric lesions may be the possible factors involved in the beneficial effects of capsaicin.

mRNA expression of cytokines in the normal gastric surface mucous epithelial cell line GSM06 during *Helicobacter pylori* and *Helicobacter felis* infection

Introduction

Cytokines are small molecular weight proteins playing important triggering role in the development of immune mechanisms in different diseases via acting on a variety of leukocytes and other cells. The main cytokine families are the proinflammatory (TNF-alpha, -beta, IFN-gamma, IL1-alpha, -beta, IL-6, IL-8, GM-CSF, etc.), antiinflammatory (IL-4, IL-5, IL-10, IL-13, TGF-beta, etc.) and chemotactic cytokines (chemokines) (RANTES, eotaxin, MCP1-5, MIP1-alpha, -beta, -gamma, etc.) beeing responsible for the activation of the different populations of leukocytes, for the maintainance of a balance during the development of the inflammatory process, and the recruitment of the immune cells from the periphery to the place of the inflammation respectively.

Originally the cells of the immune system were found to express and release most of these proteins, however later a wide range of other cells were shown to produce them, including the epithelial cells of the gastrointestinal tract.

Helicobacter pylori (*H. pylori*), the most important species of the Helicobacter genus, is one of the most widespread pathogenic bacterium, which can be found in about half of the world's population, and it is in causative relation with such important and common gastrointestinal diseases as chronic gastritis, peptic ulcer, mucosa associated lymphoid tissue (MALT)-lymphoma and probably gastric carcinoma in human.

Helicobacter felis (*H. felis*) is another species of the genus Helicobacter, which is commonly found in, and naturally pathogenic for canine and feline stomach. It is capable to colonise the stomach of small laboratory animals, and causes mild chronic gastritis with similar type of immune response (infiltration of Th1 dominant lymphocytes) as seen in human *H. pylori* infection, therefore it is used as a model in these animals to mimic human *H. pylori* infection, and to investigate the pathomechanism of *H. pylori*-induced chronic gastritis in human. Resembling to *H. pylori*, *H. felis* may also have a role in the development of gastric neoplasm in animal model.

From the histologic investigation of gastric biopsy samples obtained from *H. pylori* infected patients we know that there is a strong infiltration of the gastric mucosa by poly- and mononuclear leukocytes and lymphocytes during *H. pylori* infection. Furthermore both proinflammatory (TNF-alpha, IL1-alpha and beta) and chemotactic

cytokines (RANTES, MCP-1, IL-8) were found in the biopsy samples of *H. pylori* positive patients. However the cell homogenates of gastric biopsy specimens contain a huge amount of immunologically active, therefore cytokine-releasing leukocytes, so it may not be excluded that these are responsible for the cytokine expression found in the biopsy samples. In the last years more data obtained from experiments with tumour originated gastrointestinal cell lines releasing different cytokines have been published indicating that the leukocyte infiltration during *H. pylori* infection is at least partly due to the result of different proinflammatory and chemotactic cytokines released from the gastric epithelial cells themselves. However these results may not be applied without doubt to normal gastric epithelial cells, because many characteristics of the original cells change during the malignant transformation.

The establishment of a normal (non tumour derived) mouse gastric surface mucous epithelial cell line (GSM06) gave us the possibility to investigate the cytokine response of epithelial cells during Helicobacter-strains caused infection.

Aims

We aimed in these investigations:

1. To measure the mRNA expression of the proinflammatory cytokine IL1-beta, and chemotactic cytokine RANTES, eotaxin, MCP-1, MIP1-alpha and -beta with RT-PCR during infection with different number of live *H. felis* for 2 and 4 h.

2. To determine the mRNA expression of cytokines TNF-alpha with Southern-, and IL1-alpha and RANTES with Northern-blotting during live *H. pylori* infection for 24-48 h.

3. To determine the mRNA expression of cytokines TNF-alpha with Southern-, and IL1-alpha and RANTES with Northern-blotting during sonicated *H. pylori* infection for 24-48 h.

4. After obtaining the result that RANTES is upregulated during *H. pylori* infection, to check with Northern-blotting whether RANTES mRNA expression can be induced by bacterium other than *H. pylori*, namely by Escherichia coli.

5. To check also with Northern-blotting whether RANTES mRNA expression can be stimulated by recombinant human proinflammatory cytokines TNF-alpha and IFN-gamma either alone or in combination.

Materials and methods

GSM06 cells were maintained in culture dishes in DMEM/Ham's medium. When the cells reached confluence they were infected with bacterium.

The GSM06 cells were infected or treated as follows.

Infection with

1. 10^5, 10^6, 10^7, 10^8, 10^9 live *H. felis*/ml medium for 2 and 4 h.
2. 10^8 live *H. pylori*/ml medium for 36 h.
3. 10^8 sonicated *H. pylori*/ml medium for 36 h.
4. 10^8 live E. coli/ml medium for 8 h.

To check whether cytokine expression can be induced by proinflammatory cytokines, GSM06 cells were

5. treated with recombinant human TNF-alpha (100 ng/ml medium) and IFN-gamma (100 ng/ml medium) both alone and in combination for 24 h.

Cells treated with medium only for 2 h served as control during the mRNA determinations.

After infection or treatment of the cells total RNA was isolated from them, and either PCR-reaction or Southern- or Northern-blotting was performed with alpha-^{32}P-radiolabeled dCTP probes synthesized in our laboratory through the RT-PCR method. The sequences of probes were confirmed to be identical to published sequences with an automatic DNA sequencing machine. The radiolabeled probes were detected and signal densities were quantified.

Results

Infection with *H. felis*

We found that - however neither mRNA of cytokines expressed in the control dishes, i.e. there was no constitutive expression of any of these cytokines in the GSM06 cells - the mRNA of the proinflammatory cytokine IL1-beta, and chemokines RANTES, eotaxin, MCP-1, MIP1-alpha and beta was expressed during infection with different number of live *H. felis* for 2 and 4 h.

Infection with live *H. pylori*

There was a weak constitutive expression of TNF-alpha mRNA expression in GSM06 cells. After infection with live *H. pylori* for up to 36 h, we found that TNF-alpha mRNA expression showed a two stepped increase on Southern blot. The first, but slight elevation appeared at 4 h after the infection, then the expression did not change. From 18h the expression elevated again, and reached a stronger second peek at 36 h. After this the expression tended to decrease at 48 h.

IL1-alpha mRNA expression also showed a weak constitutive expression. It was also time-dependently elevated during live *H. pylori* infection. The expression started to increase after 18 h, and then continuously increased until 36 h after the incubation.

GSM06 cells did not constitutively express RANTES mRNA. However we found that live *H. pylori* induced a marked and time-dependent increase in the expression of RANTES mRNA. The elevation started at 4 h, and continuously increased until 24 h after the infection.

Infection with sonicated H. pylori

TNF-alpha mRNA expression was upregulated during the incubation with sonicated *H. pylori* with similar pattern as with the live bacterium.

However the sonicated bacterium did no stimulate the expression of IL1-alpha mRNA.

The sonicated bacterium also did not activate the cells to express RANTES mRNA during the 36 h experimental period.

Infection with E. coli

In contrast to *H. pylori*, E. coli did not induce RANTES mRNA expression during 8 h.

Treatment with recombinant human proinflammatory cytokines

Neither human recombinant TNF-alpha nor IFN-gamma alone or in combination induced RANTES mRNA expression during the 24 h experimental period.

Discussion

Our present results show that the cells of a normal (non tumour derived) gastric mucous epithelial cell line themselves express the mRNA of a wide range of cytokines with proinflammatory and chemotactic characteristics during bacterial infection with *H. pylori* and *H. felis*.

From the data of the literature and our studies we may state that gastric mucous epithelial cells express and release proinflammatory and chemotactic cytokines during *Helicobacter pylori* infection. We hypothesise the chemokines in turn attract specific immune cell from the periphery to the area of bacterial invasion. These cells then can meet the antigens specific for them. After maturing fully they may secrete cyto- and chemokines abundantly, and trigger the immune response to the infection. According to this hypothesis the epithelial cells of the gastric mucosa actively participate in the development - and probably the maintainance - of the immune response and inflammation during the bacterial infection.

Summary of the new results

In these studies we obtained the following new results.

1. 100-800 ug capsaicin (between 3.2-26 mM concentrations) given intragastrically to healthy human subjects dose-dependently inhibits gastric basal acid secretion.

2. The ID_{50} on GAS is about 400 ug.

3. The inhibitory effect of capsaicin on GAS lasts for about 1 hour.

4. 400 ug intragastric capsaicin (in 13 mM concentration) increases gastric emptying rate in healthy humans.

5. The increase in blood glucagone level is higher, and indicates a faster answer to glucose absorption during the action of 400 ug intragastric capsaicin (in 13 mM concentration).

6. There is no constitutive mRNA expression of the proinflammatory cytokine TNF-alpha, IL1-alpha and -beta, and chemotactic cytokine RANTES, eotaxin, MCP-1, MIP1-alpha and -beta in the normal mouse gastric surface mucous epithelial cell line GSM06.

7. *H. pylori* or *H. felis* infection induces the mRNA expression of each cytokine.

8. E. coli does not have RANTES mRNA stimulating effect in these cells.

9. Recombinant human TNF-alpha and IFN-gamma also does not activate the cells to express RANTES mRNA.

List of publications

Papers

A. Debreceni, B. Debreceni, Gy. Mózsik (1997) A study of the actions of naloxone and morphine on gastric acid secretion and gastric mucosal damage in the rat. J. Physiol.(Paris) 91:189-97

Debreceni A., Abdel-Salam O.M.E., Figler M., Juricskay I., Szolcsányi J., Mózsik Gy. (1999) A kapszaicin egészséges emberben gyorsítja a gyomor kiürülését. Magy. Belorv. Arch. 52:103-6.

Gy. Mózsik, **A. Debreceni**, O.M.E. Abdel-Salam, I. Szabó, M. Figler, A. Ludány, I. Juricskay, J. Szolcsányi (1999) Small doses of capsaicin given intragastrically inhibit gastric basal acid secretion in healthy human subjects. J. Physiol.(Paris) 93:433-6

O.M.E. Abdel-Salam, **A. Debreceni**, Gy. Mózsik, J. Szolcsányi (1999) Capsaicin-sensitive afferent sensory nerves in modulating gastric mucosal defense against noxious agents. J. Physiol.(Paris) 93:443-54

A. Debreceni, O.M.E. Abdel-Salam, M. Figler, I. Juricskay, J. Szolcsányi, Gy. Mózsik (1999) Capsaicin increases gastric emptying raate in healthy human subjects measured by ^{13}C-labeled octanoic acid breath test. J. Physiol.(Paris) 93:455-60

O.M.E. Abdel-Salam, **A. Debreceni**, J. Szolcsányi, Gy. Mózsik (1999) Capsaicin inhibits the pentagastrin-stimulated gastric acid secretion in anaesthetized rats with acute gastric fistula. J. Physiol.(Paris) 93:461-6

F. Pakodi, O.M.E. Abdel-Salam, **A. Debreceni**, Gy. Mózsik (2000) Helicobacter pylori. One bacterium and a broad spectrum of human disease! An overview. J. Physiol.(Paris) 94:139-52

H. Nakase, K. Okazaki, Y. Tabata, S. Uose, M. Ohana, K. Uchida, T. Nishi, **A. Debreceni**, T. Itoh, C. Kawanami, M. Iwano, Y. Ikada, T. Chiba (2001) An oral drug delivery system targeting immune-regulating cells ameliorates mucosal injury in trinitrobenzene sulfonic acid-induced colitis. J. Pharmacol. Exp. Ther. 297:1122-8

M. Ohana, K. Okazaki, C. Oshima, **A. Debreceni**, T. Nishi, K. Uchida, S. Uose, H. Nakase, Y. Matsushima (2001) A critical role for IL-7R signaling in the development of Helicobacter felis-induced gastritis in mice. Gastroenterol. 121:329-36

A. Debreceni, K. Okazaki, Y. Matsushima, M. Ohana, H. Nakase, K. Uchida, S. Uose, T. Chiba - mRNA expression of cytokines and chemokines in the normal gastric surface mucous epithelial cell line GSM06 during bacterial infection with Helicobacter felis. J. Physiol.(Paris) (in press)

O.M.E. Abdel-Salam, **A. Debreceni**, J. Szolcsányi, Gy. Mózsik - Gastric mucosal damage and its prevention. Role of gastric mucosal blood flow. An overview. J. Physiol.(Paris) (in press)

Gy. Mózsik, O. Karádi, Á. Király, **A. Debreceni**, M. Figler, L. Nagy, A. Pár, G. Pár, G. Sütõ, Á. Vincze. - The key-role of intact vagal nerve and adrenals in the cytoprotective and general gastric mucosal integrites. J. Physiol.(Paris) (in press)

K. Uchida, K. Okazaki, **A. Debreceni**, S. Uose, H. Nakase, M. Ohana, C. Oshima, Y. Matsushima, C. Kawanami, H. Hiai, T. Masuda, T. Chiba - Analysis of cytokines in the early development of gastric secondary lymphoid follicles in *Helicobacter pylori*-infected BALB/c mice with neonatal thymectomy. Infect. Immun. (in press)

M. Inai, K. Okazaki, M. Ohana, T. Nishi, **A. Debreceni**, S. Uose, K. Uchida, H. Nakase, Y. Matsushima, T. Chiba - Coordinative overexpression of heparin binding epidermal growth factor-like growth factor and amphiregulin in the development of gastric foveolar hyperplasia in murine autoimmune gastritis. Lab. Invest. (revised version)

Book chapter

Gy. Mózsik, A. Debreceni, I. Juricskay, O. Karádi, L. Nagy; Biochemical energy backgrounds and their regulation in the gastric corpus mucosa in patients with different gastric secretory responses. In: T. Gaginella, Gy. Mózsik, K.D. Rainsford (eds.): Biochemical Pharmacology as an Approach to Gastrointestinal Disorders: Basic Science to Clinical Perspectives. Kluwer Academic Publishers, 1997. (pp. 199-223)

Posters and lectures

Balatonaliga, Hungary; June 4-8. 1996; 38th Annual Meeting of the Hungarian Gastroenterology Association; A. Debreceni, O.M.E. Abdel-Salam, Gy. Mózsik: Interrelationship between gastric acid back-diffusion and gastric mucosal protection by sucralfate, atropine and cimetidine in rat stomach. (Abstract in: Z. Gastroenterol. 5:307 (1996))

Istanbul, Turkey; May 7-10. 1997; 13th International Medical Sciences Student Congress; A. Debreceni, O.M.E. Abdel-Salam, Gy. Mózsik: The effect of capsaicin on the ulcer-aggravating effect of morphine in the HCl-model in the rat.

Balatonaliga, Hungary; June 4-7. 1997; 39th Annual Meeting of the Hungarian Gastroenterology Association; A. Debreceni, O.M.E. Abdel-Salam, Gy. Mózsik: The mediation of the effect of morphine in the HCl-model in the rat. (Abstract in: Z. Gastroenterol. 5:311 (1997))

Pécs, Hungary; Sept. 18-20. 1996; Fourth Congress of the International Brain Gut Society; A. Debreceni, B. Debreceni, Gy. Mózsik: Has any effect of the opioid-receptor antagonist naloxone on gastric mucosal damage induced by indomethacin, ethanol and HCl in the rat? (Abstract in: Dig. Dis. Sci. 42:1, P213 (1997))

Hong Kong, China; December 12-17. 1997; Alimentary Disease Week Hong Kong; A. Debreceni, O.M.E. Abdel-Salam, Gy. Mózsik: Morphine influences the ulcerogenic effect of acid through capsaicin sensitive primary afferent nerves in the rat. (Abstract in: J. Gastroenterol. Hepatol. 12(Suppl.):A221 (1997))

Hong Kong, China; December 12-17. 1997; Alimentary Disease Week Hong Kong; Gy. Mózsik, B. Bódis, A. Debreceni, O. Karádi, A. Király, Gy. Rumi, G. Sütő, I. Szabó, A. Vincze: Similarities and differences of gastric mucosal protection produced by PGI2 and carotene in rats treated with ethanol, HCl and indomethacin. (Abstract in: J. Gastroenterol. Hepatol. 12(Suppl.):A146 (1997))

Cairo, Egypt; February 11-14. 1998; 6th Annual International Ain Shams Medical Students' Congress; A. Debreceni, Gy. Mózsik: The effect of the mast-cell stabilizer ketotifen on the ulcerogenesis induced by ethanol, HCl and indomethacin in the rat.

Bükfürdő, Hungary; June 4-6. 1998; Magyar Belgyógyász Társaság Dunántúli Szekciójának XLV. Vándorgyűlése; Debreceni A., Juricskay I., Abdel-Salam O.M.E., Szolcsányi J., Mózsik Gy.:

Gyomorürülés mérése az új infravörös izotóp analizátorral (IRIS) emberben. (Abstract in: Magy. Belorv. Arch. 51(Suppl.) p.20 (1998))

Balatonaliga, Hungary; June 9-13. 1998; 40th Annual Meeting of the Hungarian Gastroenterology Association; O.M.E. Abdel-Salam, **A. Debreceni**, J. Szolcsányi, Gy. Mózsik: Capsaicin-sensitive sensory nerves modulate the gastric mucosal injurious effect of indomethacin in the rat. (Abstract in: Z. Gastroentol. 36:A1(p. 416) (1998)).

Balatonaliga, Hungary; June 9-13. 1998; 40th Annual Meeting of the Hungarian Gastroenterology Association; **A. Debreceni**, I. Juricskay, O.M.E. Abdel-Salam, J. Szolcsányi, Gy. Mózsik: Measurement of gastric emptying with the new, infrared isotope analyser (IRIS) method: capsaicin enhanced the gastric emptying rate in healthy human subjects (Abstract in: Z. Gastroentol. 36:A21(p. 421) (1998)).

Balatonaliga, Hungary; June 9-13. 1998; 40th Annual Meeting of the Hungarian Gastroenterology Association; Gy. Mózsik, **A. Debreceni**, I. Juricskay, O.M.E. Abdel-Salam, A. Ludány, J. Szolcsányi: A direct inhibitory effect of capsaicin on the gastric basal secretory responses in healthy human subjects (Abstract in: Z. Gastroentol. 36:A81(p. 436) (1998)).

Pécs, Hungary; July 5-8. 1998; XIIth International Conference on the Physiology of Food and Fluid Intake (ICPFFI) and Annual Meeting of the Society for the Study of Ingestive Behaviour (SSIB); **A. Debreceni**, I. Juricskay, O.M.E. Abdel-Salam, J. Szolcsányi, Gy. Mózsik: Modification of gastric emptying, glucose absorption and hormon levels by small dose of capsaicin in healthy human subjects. (Abstract in: Appetite, 31, p.304)(1998))

Pécs, Hungary; July 23-25. 1998; Section of IUPHAR GI Pharmacology Symposium; O.M.E. Abdel-Salam, **A. Debreceni**, J. Szolcsányi, Gy. Mózsik: Afferent sensory nerves in modulating gastric mucosal defense against noxious injury. (Abstract in: Dig. Dis. Sci. 43. 10. A1 (p.2339)(1998)

Pécs, Hungary; July 23-25. 1998; Section of IUPHAR GI Pharmacology Symposium; **A. Debreceni**, I. Juricskay, M. Figler, O.M.E. Abdel-Salam, J. Szolcsányi, Gy. Mózsik: A direct stimulatory effect of small dose of capsaicin on gastric emptying rate in healthy human subjects measured by 13C-labeled octanoic acid breath test. (Abstract in: Dig. Dis. Sci. 43. 10. A12 (p.2341)(1998))

Pécs, Hungary; July 23-25. 1998; Section of IUPHAR GI Pharmacology Symposium; Gy. Mózsik, **A. Debreceni**, I. Juricskay, M. Figler, O.M.E. Abdel-Salam, J. Szolcsányi: A direct inhibitory effect of small dose of capsaicin on gastric basal secretory responses in healthy human subjects. (Abstract in: Dig. Dis. Sci. 43. 10. A29 (p.2346)(1998))

Pécs, Hungary; July 23-25. 1998; Section of IUPHAR GI Pharmacology Symposium; F. Pakodi, O.M.E. Abdel-Salam, **A. Debreceni**, Gy. Mózsik: Helicobacter pylori: One bacterium and a broad spectrum of human disease. An overview. (Abstract in: Dig. Dis. Sci. 43. 10. A31 (p.2346)(1998))

Vienna, Austria; Sept. 6-11. 1998; World Congressess of Gastroenterology; **A. Debreceni**, I. Juricskay, O.M.E. Abdel-Salam, J. Szolcsányi, Gy. Mózsik: The pharmacology effect of small dose of capsaicin on gastric emptying measured by the infrared isotope analyser (IRIS) in healthy human subjects. (Abstract in: Digestion 59:53 p.243. (1998)).

Dusseldorf, Germany; Nov. 1-4. 1998; Int. Brain-Gut Society Biannual Meeting; Gy. Mózsik, **A. Debreceni**, M. Figler, O.M.E. Abdel-Salam, J. Szolcsányi: Small dose of capsaicin decreases the „parietal" and increases the „non-parietal" components of gastric basal secretion in healthy human subjects.

San Diego, USA; May 21-24. 2000; Digestive Disease Week, Annual Meeting of the American Gastroenterological Association; M. Ohana, K. Okazaki, C. Oshima, T. Nishi, **A. Debreceni**, K. Uchida, S. Uose, H. Nakase, Y. Matsushima, T. Chiba: Gastric Follicular Formation by Helicobacter Pylori Infection Depends on Th2 Type Immune Responses and Strain of the Host. (Abstract in: Gastroenterol. 118(4): A744, Part I, Suppl. 2.)(2000))

San Diego, USA; May 21-24. 2000; Digestive Disease Week, Annual Meeting of the American Gastroenterological Association; M. Ohana, K. Okazaki, C. Oshima, T. Nishi, **A. Debreceni**, K. Uchida, S. Uose, H. Nakase, Y. Matsushima, C. Tsutomu: Prevention of the Development of Autoimmune Gastritis by Helicobacter Pylori Infection in Neonatally Thymectomized Mice. (Abstract in: Gastroenterol. 118(4): A744, Part I, Suppl. 2.)(2000))

San Diego, USA; May 21-24. 2000; Digestive Disease Week, Annual Meeting of the American Gastroenterological Association; K. Uchida, K. Okazaki, T. Nishi, **A. Debreceni**, S. Uose, H. Nakase, Y. Matsushima, C. Kawanami, T. Chiba: Carbonic Anhydrase II and Th1 Type Cd4-Positive Cells Are Involved in the Development of Autoimmune-Related Pancreatitis in an Animal Model. (Abstract in: Gastroenterol. 118(4): A170, Part I, Suppl. 2.) (2000))

San Diego, USA; May 21-24. 2000; Digestive Disease Week, Annual Meeting of the American Gastroenterological Association; S. Uose, K. Okazaki, T. Nishi, **A. Debreceni**, K. Uchida, H. Nakase, M. Ohana, Y. Matsushima, M. Inai, T. Chiba: Gastric Mucosa May Be a Priming Site Against Helicobacter Pylori in the Peyer's Patch-Deficient Mice. (Abstract in: Gastroenterol. 118(4): A329, Part I, Suppl. 2.) (IF: 12.182) (2000))

Budapest, Hungary, October 25-29. 2000; 10th International Conference on Ulcer Research and 5th International Symposium on Cell Injury and Protection in the Gastrointestinal Tract: From Basic Sciences to Clinical Perspectives; **A. Debreceni**, K. Okazaki, Y. Matsushima, M. Ohana, H. Nakase, K. Uchida, S. Uose, T. Chiba: mRNA expression of cytokines in the normal gastric surface mucous epithelial cell line GSM06 during Helicobacter felis infection. (Abstract in: Dig. Dis. Sci., 46(3) (2001) p.680)

Budapest, Hungary, October 25-29. 2000; 10th International Conference on Ulcer Research and 5th International Symposium on Cell Injury and Protection in the Gastrointestinal Tract: From Basic Sciences to Clinical Perspectives; O.M.E. Abdel-Salam, **A. Debreceni**, J. Szolcsányi, Gy. Mózsik: Gastric mucosal damage and its prevention. Role of gastric mucosal blood flow. An overview. (Abstract in: Dig. Dis. Sci., 46(3) (2001) p.700)

Budapest, Hungary, October 25-29. 2000; 10th International Conference on Ulcer Research and 5th International Symposium on Cell Injury and Protection in the Gastrointestinal Tract: From Basic Sciences to Clinical Perspectives; O.M.E. Abdel-Salam, **A. Debreceni**, Gy. Mózsik, J. Szolcsányi: The effect of capsaicin on the cysteamine-induced duodenal ulcer in the rat. (Abstract in: Dig. Dis. Sci., 46(3) (2001) p.695)

Budapest, Hungary, October 25-29. 2000; 10th International Conference on Ulcer Research and 5th International Symposium on Cell Injury and Protection in the Gastrointestinal Tract: From Basic Sciences to Clinical Perspectives; Gy. Mózsik, O. Karádi, Á. Király, **A. Debreceni**, M. Figler, L. Nagy, A. Pár, G. Pár, G. Sütő, Á. Vincze. The key-role of intact vagal nerve and adrenals in the cytoprotective and general gastric mucosal integrites. (Abstract in: Dig. Dis. Sci., 46(3) (2001) p.692)

Balatonaliga, Hungary, June 5-9. 2001; 43rd Annual Meeting of the Hungarian Gastroenterology Association; **A. Debreceni**, K. Okazaki, Y. Matsushima, M. Ohana, H. Nakase, K. Uchida, S. Uose, T. Chiba. Cytokine mRNA expression in gastric epithelial cells during Helicobacter pylori infection. (Abstract in: Z. Gastroenterol. 39 (2001))