The previous studies demonstrated the pivotal role of capsaicin-sensitive peptidergic sensory neurons and vagal nerves in the maintenance of gastric mucosal integrity. The aim of the present study was: 1) to examine the effect of the functional ablation of sensory neurons with neurotoxic dose of capsaicin and surgical vagotomy on the course of healing of gastric ulcer in rat, and 2) to compare the ulcer healing action of leptin in rats with or without capsaicin-induced inactivation of sensory neurons. Three series of experiments (A, B and C) were performed in Wistar rats with gastric ulcers induced by acetic acid method. In series A, the course of ulcer healing was compared in rats with intact and capsaicin-inactivated sensory neurons. In the series B, the effect of vagotomy on the ulcer healing and accompanying changes in GBF were determined at day 8 and 16 after ulcer induction. The rats of series C, consisting of animals with intact nerves or those with capsaicin-denervation, received the 7-day treatment with exogenous leptin (10 µg/kg i.p. twice daily) to check whether blockade of sensory nerves could influence the acceleration of ulcer healing by this peptide. Capsaicin-induced ablation of sensory neurons significantly delayed ulcer healing and this was accompanied by the significant fall in the GBF and the significant rise in the gastric mucosal gene expression of IL-1β and TNF-α. Vagotomy significantly delayed ulcer healing and led to decrease in GBF at ulcer margin. Treatment with exogenous leptin significantly accelerated ulcer healing, increased the GBF at ulcer margin and upregulated mRNA for iNOS and these effects were attenuated in rats with capsaicin-deactivation of sensory neurons. We conclude that: 1) vagal and sensory neurons contribute to the gastric ulcer healing process possibly due to the increase of GBF, the limitation of inflammatory response, and overexpression of TGFβ and iNOS resulting in NO release, and 2) the acceleration of ulcer healing by leptin was attenuated in animals with capsaicin-denervation suggesting an involvement of neuropeptides released from sensory afferent nerves in the ulcer healing effect of this hormone.
INTRODUCTION

Gastric mucosa is continuously exposed to potentially noxious agents. The maintenance of mucosal integrity is ensured by a complex system of interacting factors among which sensory neurons play an essential role. These neurons form a dense plexus of fibers around the submucosal arterioles that contain and release a variety of potent neuropeptides, especially calcitonin gene related peptide (1, 2). These vasodilatatory peptides released from sensory nerves and the NO synthesized and released from vascular endothelium or produced locally in the gastric epithelium are believed to interact with prostanoids in maintenance of mucosal integrity and gastroprotection against a variety of topical irritants (3, 4).

Previous studies carried out in animals treated with capsaicin, which specifically targets on afferent neurons via vanilloid receptors of type 1 (VR-1) (5, 6) documented that sensory afferent nerves play an important role in the gastric mucosal defense. Capsaicin at a low dose stimulates sensory nerves leading to the increase in gastric mucosal blood flow and enhancement of resistance of gastric mucosa against damage by obnoxious agents (7). In contrast, neurotoxic dose of capsaicin induces an irreversible, long-standing inactivation of the capsaicin-sensitive nerves with the loss of their sensory-afferent functions and their ability to release of sensory neuropeptides. This resulted in the worsening of the mucosal integrity in response to a variety of noxious stimuli (8, 9).

The vagal nerves participating in various vago-vagal reflexes (10) are responsible for the overproduction of the secretory aggressive agents (acid and pepsin) involved in the pathogenesis of peptic ulcer. Therefore, before the discovery of H. pylori as the major cause of peptic ulcer, vagotomy was used in the treatment of peptic ulcer disease with the aim of reducing of acid secretion (11). On the other hand, previous experimental evidence indicated that vagotomy weakened gastric mucosal barrier and enhanced the susceptibility of the gastric mucosa to the damage by various ulcerogens (12, 13).

Little attempts were made to determine the involvement of vagal efferent and sensory innervation in the mechanism of healing of preexisting gastric ulcers. Therefore, using animals with chronic gastric ulcers, we determined the effect of capsaicin denervation and vagotomy on ulcer healing and accompanying alterations in the GBF at ulcer margin, expression of proinflammatory cytokines (IL-1β and TNF-α), cyclooxygenases (COX-1 and COX-2) and growth factors such as TGFα in the ulcerated gastric mucosa.
MATERIAL AND METHODS

Male Wistar rats, weighing 200-250 g and fasted for 24 h were used in all studies. All procedures performed in these studies were accepted by the Local Ethical Committees at University of Medicine in Erlangen-Nuremberg, Germany and Jagiellonian University Medical College in Cracow, Poland.

Production of gastric ulcers

Gastric ulcers were produced in Wistar rats using our modification (14) of acetic method originally proposed by Okabe and Roth (15). Animals were anesthetized with ether, the stomach was exposed and a round plastic mold (6 mm in diameter) was placed tightly on the anterior serosal surface of the stomach at the antro-oxyntic border. 75 µl of 100 % acetic acid was poured into the mold and allowed to remain on the gastric wall for 25 s. This produced an immediate necrosis of the entire mucosa and submucosa (but not serosa) within the area where the acetic acid was applied, i.e. 28 mm². The excess of acetic acid was then removed and the serosa was gently washed out with saline. Our previous studies documented that these ulcers become chronic within 2 - 3 days and heal completely within 2 - 3 weeks. After the induction of acetic ulcers the animals were allowed to recover from anesthesia and received only water at the day of operation.

Effect of capsaicin denervation and vagotomy on healing of gastric ulcers

Three major series (A, B and C) of experiment were carried out. Series A was used to determine the effect of denervation of sensory neurons on ulcer healing. For this purpose, the animals were pretreated with capsaicin (Sigma Aldrich Fine Chemicals, Poznan, Poland) injected s.c. for 3 consecutive days at a dose 25, 50 and 50 mg/kg 2 weeks before the induction of chronic ulcers. All injections of capsaicin were performed under ether anesthesia to counteract the respiratory impairment associated with injection of this agent. To check the effectiveness of the capsaicin denervation, a drop of 0.1 mg/ml solution of capsaicin was instilled into the eye of each rat and the protective wiping movements were counted as previously described (16, 17). Control rats received a vehicle injection. All animals pretreated with capsaicin showed a negative wiping movement test confirming functional ablation of the capsaicin sensory neurons. Two weeks later chronic ulcers were induced in rats with denervated sensory neurons and control rats with intact sensory neurons. The ulcer area was assessed by planimetry 7 days after ulcer induction. The GBF was measured by H₂-gas clearance method.

Series B was used to determine the effect of vagotomy on the course of ulcer healing. The subdiaphragmatic vagotomy was performed immediately before the induction of chronic ulcers by acetic acid method (18,19). The ulcer area and GBF at ulcer edge were determined at day 8 and 16 after ulcer induction.

Effect of leptin on ulcer healing and GBF at ulcer margin in rats with or without capsaicin denervation

In series C, the effects of exogenous leptin (19) on ulcer healing and the GBF at ulcer margin were determined. The following treatment groups of rats with chronic ulcers were used; 1) rats with intact sensory neurons treated with vehicle (saline) i.p.; 2) rats with intact sensory neurons treated with leptin 10 µg/kg i.p. twice daily for 7 days; 3) rats with deactivated sensory neurons treated with vehicle (saline) i.p. twice daily for 7 days after ulcer induction and 4) rats with deactivated sensory neurons treated twice daily with leptin 10 µg/kg i.p. for 7 days after ulcer induction. The ulcer area and GBF were measured at day 8 after ulcer induction as described below.
Measurement of GBF by \( H_2 \)-gas clearance method

GBF was measured at day 8 after ulcer induction, using a \( H_2 \)-gas clearance technique as described previously (8, 14). At day 8 after ulcer induction, the rats were lightly anesthetized with ether, the abdomen was opened and the stomach was exposed to measure GBF at the ulcer margin. Double needle electrodes were inserted through the serosa into the ulcer margin and into the intact oxyntic mucosa. One electrode was used for the generation of \( H_2 \) gas and the other for the measurement of tissue \( H_2 \). With this method the \( H_2 \) generated is carried away by the blood, and the polarographic current detector gives the decreasing tissue \( H_2 \) content as the clearance curve, which is then used to calculate the blood flow rate in the tissue. The blood flow was expressed as the percentage of the basal flow recorded in the gastric mucosa of control rats with saline applied to the serosa through the plastic mold.

Reverse transcription-polymerase chain reaction (RT-PCR) for detection of messenger RNA (mRNA) for leptin, cNOS and iNOS

The extraction of total RNA from gastric ulcerated tissues and control tissues was carried out using TRIZOL reagent (Gibco BRL) based on the method described by Chromczynski and Sacchi (20). Following precipitation, RNA was resuspended in RNAse-free water and its concentration was estimated by absorbance at 260 nm wavelength. Furthermore, the quality of each RNA sample was determined by running the agarose-formaldehyde electrophoresis. RNA samples were stored at -80°C until analysis.

Single stranded cDNA was generated from 5 µg of total cellular RNA using Moloney murine leukemia virus reverse transcriptase (MMLV-RT) and oligo-(dT) primers (Stratagene, Heidelberg, Germany). Briefly, 5 µg of total RNA was uncoiled by heating (65 °C for 5 min) and then reverse transcribed (37 °C for 1 h) into complementary DNA (cDNA) in a 50 µl reaction mixture that contained 50 U MMLV-RT, 0.3 µg oligo-(dT)-primer, 40 U RNase Block Ribonuclease Inhibitor, 2 µl of a 100 mM mixture of dNTPs, and 5 µl of buffer (10 mM Tris-HCl, 50 mM KCl, 5 mM MgCl\(_2\), pH = 8.3). The resultant cDNA (2 µl) was amplified in a 50 µl reaction volume containing 2 U Taq polymerase, dNTP (200 µM each), 1.5 mM MgCl\(_2\), 5 µl 10 x polymerase chain reaction buffer (50 mM KCl, 10 mM Tris-HCl, pH = 8.3) and specific primers used at final concentration of 1 mM (all reagents from Takara, Shiga, Japan). The polymerase chain reaction mixture was amplified in a DNA thermal cycler (MJ Research, PTC 200, Watertown, Massachusetts, USA) and the incubation and thermal cycling conditions were as followed: denaturation at 94 °C for 1 min, annealing at 60 °C for 45 sec and extension 72 °C for 2 min. The number of cycles was 27 for β-actin, 30 for COX-1, 33 for IL-1β, TNF-α, COX-2, cNOS and 35 for iNOS. The nucleotide sequence of the primers were as followed: β-actin, sense 5’-GAT CTT GAT CTT GCT AGG-3’; antisense 5’-TTG TAA CCA ACT GGG ACG ATA TGG-3’; cNOS sense 5’-TAC TTG AGG ATG TGG CTG-3’; antisense 5’-GTC TTC TTC CTG GTG ATG-3’; iNOS sense 5’-CAG TGG TAA CCA CAT CAG GTC-3’; antisense 5’-GTT CTC GGA CTC CAA TCT-3’; TGFα sense 5’-ATG GTC CCC GGC GCC GGA CA 3’; TGFα antisense 5’-ATG GTC CCC GGC GCC GGA CA-3’; COX-1 sense 5’-AGC CCC TCA ACC CAT TTG-3’; COX-1 antisense 5’-CAG GGA CGC CTG TTC TAC CG-3’; COX-2 sense 5’-ACA ACA TTC CCT TCC TTC C 3’; COX-2 antisense 5’-CCT TAT TTC CTT CTA CAC C-3’; IL-1β sense 5’-GCT ACC TAT GTC TTG CCC GT 3’; IL-1β antisense 5’-GAC CAT TGC TGT TTC TCG AGG-3’; TNFα sense 5’-TAC TGA ACT TCG GGG TGA TGT GTG C 3’; TNFα antisense 5’-CAG CTT TGT CCC TTG AAG AGA ACC-3’. The primer sequences for β-actin, cNOS, iNOS; TGFα, COX-1, COX-2, IL-1β and TNF-α were based on the sequences of the published cDNAs and were synthesized by GIBCO BRL/Life Technologies (Eggenstein, Germany) (19, 21). Polymerase chain
reaction products were detected by electrophoresis on a 1.5 % agarose gel containing ethidium bromide. Location of predicted products was confirmed by using 100-bp ladder (Takara, Shiga, Japan) as a standard size marker. The gel was then photographed under UV transillumination. The intensity of PCR products was measured using video image analysis system (Kodak Digital Science). The signal for PCR products was standardized against that of the β-actin mRNA from each sample and the results were expressed as PCR product/β-actin mRNA ratio.

**Western blot analysis for PECAM-1**

Shock frozen tissue from rat stomach was homogenized in 0.8 ml of lysis buffer (0,06 M Tris-HCl, pH 6.8, 10 % glycerol, 2 % SDS, 5% 2-mercaptoethanol, 0.0025% bromophenol blue). The mixture was run through a needle to shear the DNA (reduce the viscosity), heated at 95°C for 5 min. and then centrifuged at 15 000 rpm for 2 min. at 4°C. The supernatant was transferred to a new tube for protein analysis. Approximately 10 µg of total protein extracts were loaded on SDS-polyacrylamide gels and run 40 mA, followed by transfer on nitrocellulose membrane (Protran, Schleicher&Schuell, Germany) by electroblotting. 3% BSA (Sigma Aldrich, Germany) in TBS/Tween-20 buffer (137 mmol NaCl, 20 mmol Tris-HCl, pH 7.4, 0.1 % Tween-20) was used to block filters for at least 1 h at room temperature. Specific primary antibody against PECAM-1 (goat polyclonal, dilution 1:500; Santa Cruz, USA) or β-actin (mouse monoclonal, dilution 1:1000; Sigma Aldrich, Germany) was added to the membrane, followed by an anti-goat-IgG or anti-mouse-IgG HRP-horseradish peroxidase conjugated secondary antibody (dilution 1:20 000 or 1:30 000) dissolved in 1% non-fat milk in TBS-Tween-20 buffer. Incubation of primary antibody was followed by 3 washes with TBS-Tween-20 buffer for 5 min. incubation of the secondary antibody was followed by 6 washes for 5 min. Immunocomplexes were detected by the SuperSignal West Pico Chemiluminescent Kit (Pierce, USA). Thereafter, the developed membrane was exposed to an X-ray film (Kodak, Wiesbaden, Germany). Comparison between different treatment groups was made by determining the PECAM-1/β-actin ratio of the immunoreactive area by densitometry.

**Statistical analysis**

All values are expressed as mean ± of SEM. Statistical analysis was determined by the non-parametric Mann-Whitney test and Friedman two-way analysis of variance. Differences were considered statistically significant at value of p<0.05.

**RESULTS**

*Fig. 1* shows the mean ulcer area and changes in the GBF at ulcer margin 7 days after ulcer induction. In rats with functional ablation of sensory nerves, a significant delay in ulcer healing was observed and this effect was accompanied by a significant fall in GBF at ulcer margin.

*Fig. 2* demonstrates the changes in the gastric mucosal gene expression of proinflammatory cytokines, TNF-α and IL-1β, in rats with intact gastric mucosa and those with gastric ulcer with or without functional ablation of sensory nerves induced by capsaicin. In intact gastric mucosa the expression of both TNF-α and IL-1β was negligible. Conversely, in ulcerated gastric mucosa increased mRNA levels of TNF-α and IL-1β were detected. The signal intensities for TNF-α and IL-1β mRNA were significantly higher in ulcerated mucosa and this was further
**Fig. 1.** Effect of denervation of sensory nerves induced by large dose of capsaicin (125 mg/kg s.c. administered within three days) on mean ulcer size of acetic acid ulcers and gastric blood flow (GBF) at the ulcer edge at day 7 after ulcer induction. Asterisk indicates a significant change as compared to the value obtained in the vehicle-treated rats with intact sensory nerves. Mean ± SEM of 6 rats.

**Fig. 2.** Expression of IL-1β and TNF-α mRNA in the intact gastric mucosa (lane 1), in vehicle-treated mucosa around the gastric ulcer induced by the acetic acid method in rats with intact (lane 2) and functionally ablated sensory nerves by capsaicin (125 mg/gk s.c.) (lane 3). M-DNA size marker. Mean ± SEM of 6 rats. Densitometric assessment of ratio of IL-1β mRNA- and TNF-α mRNA/β-actin mRNA. Asterisk indicates a significant change as compared to intact gastric mucosa. Cross indicates a significant change as compared to vehicle-treated animals with intact sensory nerves.
significantly enhanced in gastric mucosa of rats with deactivated sensory nerves as compared to those with intact sensory nerves.

Fig. 3 summarizes the effect of capsaicin-denervation of sensory nerves on the gastric mucosal expression of COX-1 and COX-2 - two isoforms of a key enzyme in the prostaglandin biosynthesis. COX-1 expression was detected in the intact gastric mucosa. In both groups of rats with intact and denervated sensory nerves the expression of COX-1 did not change significantly after 7 days upon ulcer induction as compared to those with intact sensory nerves. In contrast, the expression of COX-2 was negligible in the intact gastric mucosa, but appeared as a strong signal in the ulcerated gastric mucosa of rats with or without capsaicin denervation.

Fig. 4 shows the effect of capsaicin denervation on the gastric mucosal expression of TGFα. In rats with intact sensory nerves, a significant increase in mRNA for TGFα was detected. This increase in TGFα mRNA expression was significantly attenuated in gastric mucosa of capsaicin-denervated animals.

Fig. 5 shows the expression of PECAM-1 protein, which is considered as an important marker of angiogenesis in the ulcerated mucosa. PECAM-1 was overexpressed in vehicle-treated gastric mucosa at the ulcer margin and this effect
**Fig. 4.** Expression of TGF-α mRNA in the intact gastric mucosa (lane 1), ulcerated gastric mucosa in rats with intact (lane 2) and functionally ablated sensory nerves by capsaicin (lane 3). M-DNA size marker. Mean ± 6 rats. Densitometric assessment of TGF-α mRNA/β-actin mRNA ratio. Gastric ulcers were induced by acetic acid method in rats with or without functional ablation of capsaicin applied s.c. in a dose of 125 mg/kg about two weeks prior ulcer induction. Asterisk indicates a significant change as compared to the value obtained in intact gastric mucosa. Cross indicates a significant change as compared to the value obtained in vehicle-treated rats with intact sensory nerves.

**Fig. 5.** Protein expression of PECAM-1 (left panel) in mucosa around the gastric ulcer induced by the acetic acid technique in rats with intact sensory nerves treated with vehicle and those with functional ablation of sensory nerves by capsaicin applied in a large dose of 125 mg/kg s.c. about two weeks prior to ulcer induction. Densitometry analysis of the ratio of PECAM-1 protein over β-actin protein is shown on right panel. Asterisk indicates a significant change as compared to the vehicle-control value.
was significantly attenuated in rats with capsaicin-induced deactivation of sensory nerves.

The effect of vagotomy on ulcer healing is shown in the Fig. 6. Following the vagotomy, the ulcer healing was significantly delayed at day 8 (13,6 mm$^2 \pm 3,18$ mm$^2$ in vagotomized vs. 7,69 mm$^2 \pm 1,46$ mm$^2$ in sham-operated control animals) and at day 16 (12,45 mm$^2 \pm 2,36$ mm$^2$ in vagotomized vs.4,72 mm$^2 \pm 1,15$ mm$^2$ in sham-control animals) after ulcer induction. The delay in ulcer healing in
vagotomized animals was accompanied by a significant decrease in the GBF as compared to that in sham-operated control animals at day 8 and 16.

Fig. 7 demonstrates the effect of vehicle (saline) and leptin on ulcer healing and GBF at ulcer margin in rats with or without functional ablation of sensory nerves induced by capsaicin. In rats with intact sensory nerves, leptin significantly accelerated ulcer healing and significantly raised GBF at ulcer margin as compared to the respective values in vehicle-control animals. In contrast, the acceleration of ulcer healing and accompanying rise in the GBF at ulcer margin observed in leptin-treated animals were significantly diminished in rats with capsaicin-induced functional ablation of sensory nerves.

As shown in Fig. 8, the strong signal for iNOS mRNA was traced in the intact gastric mucosa but cNOS expression was not detected. In vehicle-treated animals with gastric ulcer, a significant upregulation of iNOS mRNA and fall in cNOS mRNA expression were recorded in the ulcerated gastric mucosa as compared to those traced in intact gastric mucosa. Treatment with leptin produced a further significant rise in iNOS mRNA expression and a caused a further downregulation..
of mRNA for cNOS as compared with those detected in the vehicle-treated gastric mucosa in rats with intact sensory nerves. The ratio of cNOS or iNOS mRNA over β-actin mRNA were significantly lower in gastric mucosa of capsaicin-denervated animals as compared to respective values in gastric mucosa of vehicle-treated animals with intact sensory nerves. The leptin-induced upregulation of mRNA for iNOS in rats with intact sensory nerves was significantly attenuated in rats with capsaicin-denervation while the ratio of cNOS mRNA over β-actin mRNA reached the value similar to that recorded in leptin-treated animals without capsaicin denervation.

**DISCUSSION**

This study demonstrates that the functional ablation of sensory afferent nerves by capsaicin and vagotomy delay ulcer healing indicating that both intact vagal nerves and capsaicin-sensitive sensory nerves play an important role in the healing of preexisting gastric ulcers. These results remain in agreement with our and other previous studies implicating the importance of intact sensory innervation in healing of acute and chronic gastric lesions (22, 23).

The mechanism behind the delay in ulcer healing in rats with denervation of sensory nerves seems to be multifactorial and involves, as shown in this study, a variety of different factors including decrease in GBF, increased expression of proinflammatory cytokines, inhibition of angiogenesis and attenuation of mucosal gene expression of TGFα.

The present study confirmed the importance of GBF which was enhanced at ulcer margin during healing of chronic gastric ulcerations in rats with intact sensory nerves and our present observation remains in keeping with the previous findings in the respect (24). However, the denervation of sensory neurons achieved with the large dose of capsaicin led to a significant reduction in hyperemic response observed at the ulcer margin, possibly causing an impairment of the supply with oxygen and nutrients to the ulcer area and finally resulting in a delay in ulcer healing. Furthermore, the denervation of sensory neurons with a neurotoxic dose of capsaicin caused upregulation of mRNA for proinflammatory cytokines such as IL-1β and TNF-α and this could also explain the delay in ulcer healing through the inhibitory effect on cell proliferation and suppression of angiogenesis and microcirculation at the ulcer margin by these cytokines (16, 25, 26). This finding supports the notion that sensory nerves limit inflammatory response in the ulcerated mucosa as well as in other tissues as proposed previously (2, 16).

Another important mechanisms by which the denervation of sensory neurons can delay ulcer healing could be the inhibition of gastric mucosal expression of TGFα which has been proposed to play a major role in the maintenance of gastric mucosal integrity and to participate in the mechanism of ulcer healing via the
stimulation of cell proliferation and migration, and the enhancement in the GBF at the ulcer edge (14, 27, 28). In the present study, we found, for the first time, that the expression of TGFα was significantly decreased in the gastric mucosa of rats subjected to capsaicin denervation, which could be, at least in part, explanatory for the delay in ulcer healing observed in these animals. Our finding also suggests a possible interaction between sensory nerves and a major gastric mucosal integrity growth factor such as TGFα in the mechanism of ulcer healing. The importance of this cross-talk between sensory neurons and gastric mucosal growth factors such as TGFα, is emphasized by the recent evidence that the gastroprotective action of TGFα involves stimulation of capsaicin-sensitive sensory neurons (28). It seems likely that this interaction works in two both directions, the presence of sensory nerves is important for the increased expression of TGFα during ulcer healing, and vice-versa, the healing properties of TGFα could be mediated by the stimulation of capsaicin-sensitive sensory neurons and release of CGRP by this growth factor (28, 29).

Results of the present study indicate that capsaicin denervation of sensory neurons attenuates the action of satiety hormone such as leptin, which has recently been implicated in the mechanism of the ulcer healing (29). Our group provided the evidence that leptin generated and released from the stomach, exhibits gastroprotective activity and accelerates in dose-dependent manner the ulcer healing (19, 29). Moreover, these ulcer healing properties of leptin are mediated, at least partly, by NO released into gastric lumen by this hormone (30). In this paper, we confirmed that leptin accelerated the ulcer healing, and this effect was accompanied by a significant upregulation of iNOS mRNA expression with concomitant increase in GBF at the ulcer margin. However, the capsaicin-induced denervation of sensory nerves significantly attenuated the stimulatory effect of leptin on iNOS mRNA expression. It is of interest that leptin produced the rise in the iNOS expression while causing downregulation of mRNA for cNOS in the gastric mucosa of rats with intact sensory nerves and in those with capsaicin denervation. This suggests that dramatic overexpression of iNOS, especially in rats with intact sensory nerves may compensate for the effect of cNOS downregulation induced by leptin and that iNOS serves as major enzymatic source of NO in the mechanism of acceleration of ulcer healing by leptin but this hypothesis requires additional experimental evidence.

One of the important findings of this study is the observation that the vagotomy delayed significantly ulcer healing. Since the hyperemic response at the ulcer edge was significantly attenuated after the vagotomy, it is likely that that vaso-vagal reflexes (10) are activated by the gastric ulcer and possibly involve the release of NO and neuropeptides such as calcitomin gene related peptide (CGRP) that could contribute to the ulcer healing. Another possible mechanism behind the delayed ulcer healing in vagotomized rats could be decreased gastric emptying playing an important role in ulcer healing (30, 31). However, the precise
molecular mechanisms responsible for this phenomenon need to be clarified in future studies.

We conclude that vagal and sensory nerves contribute to the ulcer healing. The sensory nerves are involved in ulcer healing probably via increase of GBF, stimulation of mucosal TGFα expression and release of NO due to the activation of iNOS and possibly CGRP. The action of leptin is attenuated in rats with capsaicin-deactivated sensory neurons indicating that gastroprotective and ulcer healing properties of leptin require intact vagal and sensory innervation of the stomach.

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Received: February 5, 2004
Accepted: March 1, 2004

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