Role of cyclooxygenase-2 in Helicobacter pylori-induced gastritis in Mongolian gerbils

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Takahashi, Satoru, Takuya Fujita, and Akira Yamamoto. Role of cyclooxygenase-2 in Helicobacter pylori-induced gastritis in Mongolian gerbils. Am J Physiol Gastrointest Liver Physiol 279: G791–G798, 2000.—Cyclooxygenase (COX)-2 expression is induced in the gastric mucosa of Helicobacter pylori-infected patients, but its role remains unclear. We examined the effects of NS-398 and indomethacin on gastric pathology in H. pylori-infected Mongolian gerbils. COX-1 was detected in both normal and H. pylori-infected mucosa, whereas COX-2 was expressed only in the infected mucosa. PGE2 production was elevated by H. pylori infection, and the increased production was reduced by NS-398, which did not affect PGE2 production in normal mucosa. Indomethacin inhibited PGE2 production in both normal and infected mucosa. Hemorrhagic erosions, neutrophil infiltration, lymphoid follicles, and epithelium damage were induced by H. pylori infection. NS-398 and indomethacin aggravated these pathological changes but did not increase viable H. pylori number. H. pylori-increased production of neutrophil chemokine and interferon-γ was potentiated by NS-398 and indomethacin. Neither NS-398 nor indomethacin caused any pathological changes or cytokine production in normal animals. These results indicate that COX-2 as well as COX-1 might play anti-inflammatory roles in H. pylori-induced gastritis.

Prostaglandin; nonsteroidal anti-inflammatory drug; infection

HELICOBACTER PYLORI is recognized as a major etiologic factor of chronic gastritis and gastric/duodenal ulcers. H. pylori infection causes marked infiltration of inflammatory cells into the gastric mucosa and expression of many cytokines. Consequently, it is generally suspected that cytokine-related inflammatory responses might be involved in H. pylori-induced mucosal injuries (3, 5, 10, 43). Similarly, mucosal defense mechanisms might also be activated by H. pylori infection. Prostaglandins (PGs) are well-known mucosal defense factors, protecting the gastric mucosa against injury caused by a variety of toxic stimuli (9, 28). PGE2 stimulates the secretion of gastric mucus and bicarbonate, increases mucosal blood flow, inhibits acid secretion, and reduces gastric motility (9). PGs are synthesized through cyclooxygenase (COX), which is a target of nonsteroidal anti-inflammatory drugs (NSAIDs) (38). COX exists in two isoforms, of which COX-1 is constitutively expressed in many tissues, including the stomach, and COX-2 is normally undetectable in most tissues, its expression being induced at inflammatory sites (13, 23). In the normal gastric mucosa, COX-1-derived PGs play a crucial role in maintaining mucosal integrity (14, 18). In contrast, COX-2 is not expressed in normal mucosa, but its induction results in a marked and sustained increase in PGE2 production in the damaged mucosa (24, 32, 37). In addition to COX-1, COX-2 also plays an important role in the healing of gastric ulcers (24, 32). Recent studies showed that COX-2 expression is observed in the gastric mucosa of H. pylori-positive patients (22, 31, 33). In addition, Romano et al. (29) reported that H. pylori directly induces COX-2 mRNA expression and increases PGE2 production in gastric cancer MKN28 cells. However, the role of COX-2 in H. pylori-induced gastritis in vivo remains unclear.

Mongolian gerbil models of H. pylori infection have been established and widely used (15, 16, 20, 21, 34). We have shown that chronic gastritis and ulcers are generated in all H. pylori-infected animals (20, 34). In addition, Watanabe et al. (41) recently reported that gastric cancers are also developed by H. pylori infection in gerbils. Thus the gerbil model is quite suitable for in vivo study of the pathogenesis of H. pylori-induced gastric diseases, since this model exhibits pathological features that mimic those of human patients with H. pylori.

To investigate the role of COX-2 in H. pylori-induced gastritis, we examined the effect of NS-398, a COX-2-selective inhibitor, on H. pylori-induced pathological changes in Mongolian gerbils, compared with indomethacin, a nonselective COX inhibitor.

METHODS

Animals. Male Mongolian gerbils (6 wk old, 40–50 g) were kindly supplied from Nihon SLC (Hamamatsu, Japan). The animals were kept in an isolated clean room with regulated temperature (20–22°C) and humidity (~55%) with a 12:12-h light/dark cycle. The animals were fasted for 24 h before H.
**pylori** inoculation, and drinking water was also withheld after the inoculation. From 4 h after the inoculation, both food and water were freely available to the animals.

**H. pylori** preparation and inoculation of Mongolian gerbils. The preparation and inoculation of **H. pylori** were performed as we previously described (34). A *capA* - and *vacA* -positive standard strain of *H. pylori* (NCTC 11637; American Type Culture Collection, Rockville, MD) was used. The bacteria were incubated in a brain-heart infusion broth (Difco Laboratories, Detroit, MI) containing 10% fetal bovine serum (GIBCO BRL, Gaithersburg, MD) at 37°C overnight under a microaerophilic atmosphere and allowed to grow to a density of $-2.0 \times 10^8$ colony-forming units (CFU)/mL. *H. pylori* (2.0 $\times 10^9$ CFU; 1.0 ml) was orally administered to each animal. Normal animals received 1.0 ml of the medium alone.

**Western blot analysis of COX-1 and COX-2 proteins.** Expression of COX-1 and COX-2 proteins in the gastric mucosa was examined by Western blotting. Gastric specimens (the fundus near the antrum) were taken from normal and **H. pylori**-infected animals. COX proteins were partially purified according to the method of Gierse et al. (12). The specimens were homogenized in 25 mM Tris- HCl (pH 8.0) buffer containing 250 mM sucrose, followed by centrifugation at 10,000 $g$ for 20 min. The pellet was resuspended in 25 mM Tris- HCl (pH 8.0) buffer containing 1% 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate, and the mixture was gently stirred for 2 h at 4°C. The supernatant was recovered after centrifugation at 30,000 $g$ for 30 min and applied onto a DEAE-Sepharose CL-4B (Amersham Pharmacia Biotech, Little Chalfont, UK) column that had been equilibrated with 25 mM Tris- HCl (pH 8.0) buffer containing 0.5% 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate, 1 mM phenylmethylsulfonyl fluoride, and 0.2 mM EDTA. After the column was washed with the same buffer supplemented with 50 mM NaCl, elution was performed with 200 mM NaCl.

**Determination of viable** *H. pylori*. Viable *H. pylori* in the stomach was assayed according to our previously reported method (34). The animals were killed, and their stomachs were excised. The stomachs were homogenized in 20 ml PBS. The diluted homogenates were applied onto Brucella agar (GIBCO BRL) plates supplemented with 10% horse blood (Nippon Bio-Test, Tokyo, Japan) and (in $\mu$g/ml) 2.5 amphoterin B (Sigma, St. Louis, MO), 9 vancomycin (Sigma), 0.32 polymyxin B (Sigma), 5 trimethoprim (Sigma), and 50 2,3,5-triphenyltetrazolium chloride (Wako Pure Chemicals). The plates were incubated at 37°C under a microaerophilic atmosphere for 7 days. The number of colonies was counted, and viable *H. pylori* was expressed as CFU per stomach.

**Determination of neutrophil chemokine, interferon-$\gamma$, and interleukin-10 production.** The production of cytokine-induced neutrophil chemoattractant (CINC/KC), interleukin (IL)-8 family chemokine in rodents), interferon (IFN)-$\gamma$, and IL-10 was assayed according to the method of Noach et al. (26) with slight modifications. Gastric specimens (the fundus near the antrum) were taken from normal and *H. pylori*-infected animals. After being washed with PBS, the tissues were minced and then incubated in 1 ml of Dulbecco’s modified Eagle’s medium supplemented with 2.5% fetal bovine serum and the above antibiotics at 37°C for 20 h under 5% CO$_2$ in air. Thereafter, the tissues were homogenized in the culture medium containing 0.1 mM phenylmethylsulfonyl fluoride and 1 $\mu$g/ml leupeptin. The homogenates were centrifuged at 10,000 $g$ for 20 min. The amounts of CINC/KC, IFN-$\gamma$, and IL-10 in the resulting supernatants were determined by enzyme immunoassay (CINC/KC EIA kit; Immuno Biological Laboratories, Fujioka, Japan) and ELISA (IFN-$\gamma$ ELISA kit and IL-10 ELISA kit; Biosource International, Camarillo, CA), respectively. CINC/KC, IFN-$\gamma$, and IL-10 production was expressed as picograms per milligram tissue per h.

**Drugs.** NS-398 (kindly synthesized by Nippon Chemiphar, Tokyo, Japan) and indomethacin (Sigma) were finely dispersed in Tween 80 (10 mg/50 $\mu$l) and then suspended by adding saline to the desired concentrations. In our preliminary experiment, NS-398 at 20 mg/kg, but not at 10 mg/kg, had inhibited PGE$_2$ production in normal mucosa, indicating that 10 mg/kg NS-398 was ineffective in COX-1 activity. In addition, indomethacin even at 2 mg/kg had potently reduced PGE$_2$ levels in normal mucosa, but repeated administration of 5 mg/kg indomethacin had been lethal to *H. pylori*-infected gerbils. Therefore, the doses of 10 mg/kg and 2 mg/kg were
selected for NS-398 and indomethacin, respectively. The drugs were subcutaneously administered once daily for 4 wk from 2 wk of H. pylori infection. The animals were given the drugs in a volume of 10 ml/kg body wt. Control animals received the vehicle alone.

Statistical analysis. Data are presented as means ± SE of 3–6 animals/group. Statistical differences were evaluated by Student’s t-test or Mann-Whitney U-test. P values of <0.05 were considered significant.

RESULTS

COX-2 induction in the gastric mucosa by H. pylori infection. In our model of H. pylori infection, H. pylori is colonized for at least 10 mo in the gastric mucosa of all gerbils given the bacteria (20, 34). The number of viable H. pylori in the stomach reached a plateau level from 2 wk after the inoculation. In addition, gastritis with hemorrhagic mucosal lesions and gastric ulcers were generated only in the fundus near the antrum from 4 wk and 20 wk of the infection, respectively (20, 34). Thus the region is highly sensitive to H. pylori, and the following parameters, except for H. pylori viability, were measured in the region.

At first, we examined the expression of COX proteins and PGE2 production in the gastric mucosa during H. pylori infection (Fig. 1). On Western blot analysis, COX-1 protein was detected both in normal mucosa and in the mucosa with H. pylori infection. The level of COX-1 protein remained nearly constant during the infection. In contrast, COX-2 protein was not found in normal or H. pylori-infected (2 wk) mucosa, but H. pylori infection for 4 wk induced the expression of COX-2 protein. PGE2 production in normal mucosa was 36.7 ± 5.6 pg·mg⁻¹·h⁻¹. At 2 wk of H. pylori infection, there was no difference in PGE2 production compared with the normal level. However, PGE2 production was significantly elevated from 4 wk of the infection compared with that in normal mucosa. There was a correlation between the increase in PGE2 production and the intensity of the COX-2 protein band.

Effects of NS-398 and indomethacin on H. pylori-induced PGE2 production and gastritis. As shown in Fig. 1, the increase in PGE2 production was associated with COX-2 induction in the H. pylori-infected mucosa. To investigate the role of COX-2 in H. pylori-induced gastritis, we examined the effects of NSAIDs on PGE2 production and gastric pathology caused by H. pylori.

NS-398 (a COX-2-selective inhibitor) at 10 mg/kg or indomethacin (a nonselective COX inhibitor) at 2 mg/kg was administered for 4 wk to normal and H. pylori-infected gerbils, PGE2 production in the gastric mucosa was determined. Data are means ± SE for 6 animals/group. *Significantly different from normal value.
with NS-398 and indomethacin, although there were no significant differences between the drug-treated
and control groups. Erosive area was 1.7 ± 0.6 mm²
and 2.0 ± 0.6 mm² in NS-398- and indomethacin-
treated groups, respectively.

Neutrophil infiltration, epithelium damage, and
lymphoid follicle formation were also evaluated as
shown in Figs. 3 and 4. H. pylori infection caused
marked infiltration of neutrophils into the gastric mu-
cosa and epithelium damage. Furthermore, lymphoid
follicles were generated in the submucosa. Both NS-
398 and indomethacin significantly aggravated the H.
pylori-induced neutrophil infiltration, epithelium dam-
age, and lymphoid follicle formation. The aggravation
of neutrophil infiltration appeared to be more severe in
indomethacin-treated animals than in NS-398-treated
ones. Epithelium damage was also more significant
and lymphoid follicles more enlarged by indomethacin
than by NS-398. However, repeated administration of
NS-398 for 4 wk induced no inflammation or damage in
normal animals. Similarly, indomethacin did not cause
appreciable pathological changes in normal animals.

Effects of NS-398 and indomethacin on H. pylori
infection and the production of CINC/KC, IFN-γ, and
IL-10. Since NS-398 and indomethacin aggravated H.
pylori-induced gastritis, we determined the number of
viable H. pylori in the stomach after treatment with
the drugs. The number of H. pylori colonized in the
stomach was 2.19 ± 0.56 × 10⁵ CFU in the control
group. Both NS-398 (1.92 ± 0.42 × 10⁵ CFU) and
indomethacin (1.51 ± 0.38 × 10⁵ CFU) tended to re-
duce H. pylori number, but there were no significant
differences between the drug-treated and control
groups.

We next examined the effects of NS-398 and indo-
methacin on the production of CINC/KC (a predomi-
nant neutrophil chemokine in rodents) and IFN-γ in
the gastric mucosa (Fig. 5). H. pylori infection for 6 wk
significantly increased CINC/KC and IFN-γ production
by ~23- and ~8-fold, respectively, compared with the
production in normal mucosa. Both NS-398 and indo-
methacin significantly potentiated the H. pylori-in-
creased CINC/KC and IFN-γ production. Treatment
with NS-398 and indomethacin further promoted
CINC/KC production by 2.0- and 2.8-fold, respectively,
compared with the H. pylori-infected control group.
The IFN-γ production in the NS-398- and indometha-
tin-treated groups was also increased by 1.6- and 2.0-
fold, respectively, compared with the control with
H. pylori infection.

IL-10 was not detected in normal mucosa, whereas
its production was slightly induced by H. pylori infec-
tion (0.28 ± 0.09 pg·mg⁻¹·20 h⁻¹). However, the IL-10
production in the H. pylori-infected mucosa was not
affected by either NS-398 or indomethacin.

Neither NS-398 nor indomethacin increased the cy-
tokine production in normal animals. Similar to the
effects on gastric pathology, indomethacin had a stron-
ger effect on H. pylori-induced CINC/KC and IFN-γ
production than NS-398.

Fig. 3. Histological appearance of patho-
logical changes in the gastric mucosa of
H. pylori-infected gerbils. Vehicle (con-
trol), 10 mg/kg NS-398, or 2 mg/kg indo-
methacin was administered for 4 wk to
normal and H. pylori-infected gerbils. A:
normal mucosa. B: H. pylori-infected
mucosa in control animals. C: H. pylori-
infected mucosa in NS-398-treated ani-
mals. D: H. pylori-infected mucosa in
indomethacin-treated animals. H. pylo-
ri-induced neutrophil infiltration, lym-
phoid follicles, and epithelium damage
were aggravated by NS-398 and indo-
methacin. Magnification, ×25.
DISCUSSION

In the present study, \textit{H. pylori} infection for \(>4\) wk induced COX-2 expression in the gastric mucosa of Mongolian gerbils. Recent studies with human gastric specimens also revealed that COX-2 expression is absent in normal mucosa but is profoundly induced in \textit{H. pylori}-positive gastritis (22, 31, 33). In contrast, COX-1 protein was constitutively expressed in both normal and \textit{H. pylori}-infected mucosa of gerbils. PGE\textsubscript{2} produc-

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**Fig. 4.** Effects of NS-398 and indomethacin on \textit{H. pylori}-induced neutrophil infiltration (A), lymphoid follicle formation (B), and epithelium damage (C) in the gastric mucosa of Mongolian gerbils. Vehicle (control), 10 mg/kg NS-398, or 2 mg/kg indomethacin (IND) was administered for 4 wk to normal and \textit{H. pylori}-infected gerbils. *Significantly different between the indicated groups.

**Fig. 5.** Effects of NS-398 and indomethacin (IND) on \textit{H. pylori}-increased cytokine production in the gastric mucosa of Mongolian gerbils. After vehicle (control), 10 mg/kg NS-398, or 2 mg/kg indomethacin was administered for 4 wk to normal and \textit{H. pylori}-infected gerbils, gastric tissues were isolated, and then the production of cytokine-induced neutrophil chemoattractant (CINC/KC; A) and interferon-\(\gamma\) (IFN-\(\gamma\); B) in the tissues was determined. Data are means ± SE for 4 (normal) or 6 (infected) animals per group. *#Significantly different from control in normal and \textit{H. pylori}-infected animals, respectively.
tion was elevated with COX-2 protein expression, and the increased production was significantly inhibited by NS-398 at 10 mg/kg, at which dose PGE2 production in normal mucosa was not affected. These results indicate that COX-2 functionally contributes to the increased PGE2 production in H. pylori-infected mucosa. Similarly, COX-1 also produces PGE2 in H. pylori-infected mucosa, because 2 mg/kg indomethacin reduced PGE2 production in normal mucosa and the inhibitory effect of 2 mg/kg indomethacin on PGE2 production in H. pylori-infected mucosa was more potent than that of 10 mg/kg NS-398. Romano et al. (29) reported that adhesion of H. pylori on cultured gastric cancer MKN28 cells results in COX-2 mRNA expression. However, it is unclear whether the direct effect of H. pylori on gastric cells is crucial for COX-2 expression in vivo, because COX-2 protein was not expressed even at 2 wk of H. pylori infection in our model. COX-2 expression may result from H. pylori-associated mucosal inflammation, because 4 wk of H. pylori infection was required for gastritis and COX-2 expression. In fact, it is also known that H. pylori infection increases the expression of cytokines such as IL-1 and tumor necrosis factor-α, which serve as potent COX-2 inducers (13, 23, 37). Further investigation is needed to clarify the relationship between H. pylori infection and COX-2 induction in vivo.

In H. pylori infection, both bacterial and host factors are believed to contribute to gastric mucosal damage. Regarding host factors, it is suspected that inflammatory responses may be involved in H. pylori-induced gastritis (3, 5, 10, 43). Blaser (3) speculated that severe mucosal inflammation disrupts gastric epithelial functions and therefore might be deleterious to the mucosa. In the present study, NS-398 and indomethacin significantly promoted neutrophil infiltration and lymphoid follicle formation induced by H. pylori infection, and the effect of indomethacin was more potent than that of NS-398. The effects of the NSAIDs on inflammatory cells were associated with inhibition of mucosal PG production. These results indicate that both COX-1- and COX-2-derived PGs might suppress the host inflammatory response to H. pylori infection, i.e., PGs might exert anti-inflammatory effects in H. pylori-infected gastric mucosa. Consequently, aggravation of H. pylori-induced epithelial damage and mucosal erosions by the NSAIDs might result from potentiation of mucosal inflammation.

In response to H. pylori infection, mucosal defense mechanisms might be activated. Because PGs are important defensive factors in the gastric mucosa (9, 28), COX-2 induction is reasonable for protection of the mucosa against H. pylori. PGE2 increases blood flow and secretion of mucus and bicarbonate, inhibits acid secretion, and directly protects gastric cells against toxic stimuli (9). We reported that H. pylori infection for 2 and 4 wk causes an increase in mucus synthesis in the gastric mucosa of gerbils and that both NS-398 and indomethacin suppress the increased mucus synthesis (35). The decreases in these PG defensive responses to H. pylori infection are suggested to contribute to aggravation of mucosal inflammation caused by COX inhibition.

In addition, downregulation of proinflammatory cytokine expression by PGs is also likely to be important for mucosal protection against H. pylori infection. In the patients with H. pylori-positive gastritis, the IL-8 level in the gastric mucosa is significantly higher than in ones with H. pylori-negative gastritis (6, 42). Similarly, in our gerbil model, CINC/KC production was induced by H. pylori infection. NS-398 and indomethacin significantly potentiated CINC/KC production in H. pylori-infected mucosa. CINC/KC belongs to the IL-8 chemokine family and is considered to play a crucial role in neutrophil infiltration in rodents because rodent counterparts of IL-8 have not been identified (40). The increased CINC/KC production accounts for enhancement of neutrophil infiltration by the NSAIDs in H. pylori-infected mucosa. These results suggest that PGs, derived from COX-2 as well as COX-1, downregulate CINC/KC production, resulting in suppression of neutrophil infiltration in H. pylori-infected mucosa.

Gastric mucosal T-lymphocyte response to H. pylori infection is dependent predominantly on type 1 helper T-lymphocytes, which are characterized as IFN-γ-secreting cells (8, 10, 19). Mohammadi et al. (25) reported that in vivo neutralization of IFN-γ by administration of anti-IFN-γ antibody causes a significant reduction of gastric inflammation induced by Helicobacter felis in mice. Irisawa et al. (17) reported that H. pylori-induced mucosal damage is augmented by the overexpression of IFN-γ in the stomach of mice. Furthermore, Sawai et al. (30) reported that there is no inflammatory pathology in the gastric mucosa of H. pylori-infected IFN-γ gene-deficient mice, whereas inflammatory cell infiltration and erosions are observed in the mucosa of H. pylori-infected wild-type mice. Consequently, it has been widely accepted that IFN-γ is one of the important causal factors for H. pylori-associated diseases. We also confirmed that H. pylori infection increases IFN-γ production in gerbils and found that the increase in IFN-γ production is potentiated by NS-398 and indomethacin. Similar to the case of CINC/KC production, these results suggest that PGs, derived from both COX-1 and COX-2, downregulate IFN-γ production, resulting in an attenuation of mucosal inflammation induced by H. pylori infection.

In contrast, IL-10 production was induced by H. pylori infection, as observed in human patients (42), but was not affected by NS-398 or indomethacin. IL-10 has been shown to inhibit the production of cytokines, including IL-8 and IFN-γ (2, 7). The failure to promote IL-10 level did not attenuate the NSAID-increased production of CINC/KC and IFN-γ in H. pylori-infected mucosa. In addition, the fact that NSAIDs had no effect on IL-10 production suggests that the NSAID-induced increases in CINC/KC and IFN-γ levels are due to the increased production and do not result from the inhibition of peptidase activity during culturing.

The number of viable H. pylori in the stomach was reduced by NS-398 and indomethacin, although there
were no significant differences between the drug-treated and control groups. This result indicates that the deleterious effects of the NSAIDs on the gastric mucosa do not result from the increase in the number of viable _H. pylori_. Caselli et al. (4) reported the similar result that, in _H. pylori_-positive patients with rheumatoid arthritis, the _H. pylori_-positive rate is significantly reduced by NSAID treatment compared with the non-treated group. To our knowledge, there have been no reports that NSAIDs possess an anti-H. pylori activity, and we confirmed that the minimal inhibitory concentration of indomethacin toward _H. pylori_ is 50 μg/ml and is quite a bit higher than that of clarithromycin (0.06 μg/ml). An attenuation of mucus synthesis may be related to the decrease in _H. pylori_ number. The gastric mucus layer is known to serve as the major habitat of _H. pylori_, and NSAIDs inhibit the increased mucus synthesis in _H. pylori_-infected mucosa of gerbils. Alternatively, the increase in IFN-γ production may result in the decrease in _H. pylori_ number. In a recent study by Sawai et al. (30), the number of _H. pylori_ in the stomach in IFN-γ gene-deficient mice was higher than that in wild-type mice, suggesting that IFN-γ plays a protective role in _H. pylori_ infection. Interestingly, we found that IFN-γ, in concert with _H. pylori_, potently reduces mucus secretion by cultured gastric epithelial cells (36).

COX-2-selective inhibitors are expected as new NSAIDs without ulcerogenic effect. In fact, COX-2-selective NSAIDs such as nimesulide and celecoxib are clinically used as anti-inflammatory drugs, but the incidences of their gastric side effects are significantly lower than those of conventional NSAIDs. However, our results suggest the possibility that COX-2-selective NSAIDs may have an injurious effect on the gastric mucosa of _H. pylori_-positive patients. Wallace et al. (39) reported that, to achieve a desirable anti-inflammatory effect, COX-2-selective NSAIDs needed to be given at high doses in which both COX-1 and COX-2 activities are inhibited. If so, the safety of COX-2-selective NSAIDs may be lowered, especially in _H. pylori_-infected patients. Overall, independent of type of NSAID, NSAID users should be aware of these side effects if they are infected with _H. pylori_. In the case of application of COX-2-selective NSAIDs to preexisting gastric ulcers, the drugs also exert an unfavorable effect. We previously reported that gastric ulcer healing is significantly impaired by NS-398 at low doses in which COX-2 activity only is inhibited in rats (32).

We conclude that COX-2 as well as COX-1 has an anti-inflammatory effect in _H. pylori_-induced gastritis in Mongolian gerbils. COX-2-selective inhibitors may aggravate gastritis if used in _H. pylori_-positive patients.

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