Increasing evidence suggests that endogenously produced NO stimulates the release of PGE2 by COXs. The effect of COX activity on iNOS-NO pathway can be important in the regulation of gastric mucosal integrity in inflammatory states.

The gastric mucosa is constantly exposed to various stimulants, including acid, pepsin, alcohol, Helicobacter pylori, or drugs (e.g., nonsteroidal anti-inflammatory drugs). Among the stimulants, nonsteroidal anti-inflammatory drugs, in particular, are well recognized for being responsible for causing upper gastrointestinal complications, ranging from dyspeptic symptoms to life-threatening complicated ulcers (Hirschowitz, 1994). Increasing evidence suggests that endogenously produced NO maintains the gastric mucosal integrity in combination with prostanoids, including prostaglandins (PGs) (Whittle et al., 1990). NO and prostanoids are synthetized by nitric-oxide synthase (NOS) and cyclooxygenase (COX), respectively, both of which have constitutive and inducible isoforms (Moncada et al., 1990). NO and prostanoids are synthesized by nitric-oxide synthase (NOS) and cyclooxygenase (COX), respectively, both of which have constitutive and inducible isoforms (Moncada et al., 1991; Dubois et al., 1998). In the gastric mucosa, two types of constitutive NO synthase have been discovered by using immunohistochemical techniques: neuronal NO synthase, localized in chief cells and mucosecretory cells of the gastric epithelium, and endothelial NO synthase, localized in endothelia of the submucosal arterioles and muscularis mucosae (Fischer et al., 1999; Garcia-Vitoria et al., 2000). Inducible NO synthase (iNOS) is expressed in the cells involved in inflammation and immune activation through stimulation with certain cytokines and/or endotoxins (lipopolysaccharide; LPS). COX is the rate-
limiting enzyme for the production of PGs from arachidonic acid. COX-2 is the inducible form of COX enzyme, the synthesis of which is induced rapidly and transiently by various proinflammatory mediators and mitogenic stimuli (Clancy et al., 1998). COX-1 is a housekeeping enzyme that is constitutively expressed in the gastrointestinal tract and many other tissues (O’Neill and Ford-Hutchinson, 1993).

It has been to date demonstrated that there is a cross talk between the products of NOS and COX enzymes. First, NOS-derived NO has been shown to interact with COX pathways. However, contradictory results have been reported with respect to whether NO enhances, inhibits, or has little effect on COX activity (Goodwin et al., 1999; Coffey et al., 2001, and references therein). Second, it has also been reported that COX products interact with NOS pathway, although the results from various cells and tissues have been controversial (Tetsuka et al., 1994; Galea and Feinstein, 1999). Together, it seems that the cross talk between NOS and COX expression and activity depends on the cell type, the isoform of the enzyme, the timing and concentration of the mediator released, and/or the specificity of selective inhibitor.

Although the gastric mucosal integrity in inflammatory states can be modulated by the concerted action of endogenous NO and PGs, little is known of the cross talk effects between them, especially in vivo system. The cross talk represents an important mechanism, by which the initial inflammatory response can be amplified or attenuated and serve as a therapeutic basis to manipulate the course of an inflammatory response. In the present study, to elucidate in vivo cross talk between NO and PGs in a rat inflammatory response. In the present study, to elucidate in vivo cross talk between NO and PGs, little is known of the cross talk effects in the gastric mucosa of the LPS-treated rat. A DETC-3H2O solution (400 mg/kg; Aldrich Chemical Co., Milwaukee, WI) and an Fe-citrate mixture (40 mg/kg of FeSO4·7H2O and 200 mg/ml of sodium citrate; Wako Pure Chemicals, Osaka, Japan) were injected intraperitoneally and subcutaneously, respectively. An Fe-DETC complex thus internally formed could trap endogenously produced NO to yield an NO-Fe-DETC adduct. Thirty minutes after the trapping agent was injected, the stomach was removed under deep anesthesia. The glandular mucosa at the side of the greater curvature was selectively resected and minced. Each sample, drawn by a 1-ml plastic syringe, was collected in a glass capillary tube (75 mm in length; 46-μl inside volume), into a quartz tube (outer diameter, 5 mm). EPR spectra were recorded at ambient temperature with a spectrometer (TE-200; JEOL, Tokyo, Japan). The instrument settings were center field, 331 mT; field scan, 4 mT; sweep time, 4 min; time constant, 0.3 s; modulation amplitude, 0.32 mT; modulation frequency, 100 K; microwave power, 60 mW; and microwave frequency, ~9.5 GHz. The amplitude of the signal, which was proportional to the amount of NO, was obtained by measuring the peak-to-peak height of the lower field side signal in a three-line spectrum that is characteristic of an NO adduct. The NO adduct concentration of the Fe-DETC complex was estimated by comparing it with the signal height of a standard solution of a chemically synthesized NO complex. The concentration in tissues, estimated at 30 min after the injection of NO trapping reagent, was expressed in the unit of nanomoles per gram of tissue per 30 min.

Prostaglandin E2 Expression Assay. The mucosal contents of PGE2 were measured in the glandular gastric mucosa that had been removed, weighed, and put into a tube containing 100% ethanol plus 0.1 M indomethacin. Then, the samples were minced by scissors, homogenized, and centrifuged for 10 min at 12,000 rpm at 4°C. The supernatant of each sample was used for determination of PGE2 by enzyme immunoassay using PGE2 kit (Cayman Chemical).

Immunohistochemistry. Portions of the oxyntic gland area of the stomach were fixed in 10% buffered formalin, embedded in paraffin, and stained with hematoxylin and eosin. Serial sections cut from paraffin blocks (4 μm) were mounted on glass slides, dewaxed, and dehydrated in xylene and washed in alcohol and phosphate-buffered saline, respectively. The sections were then incubated in 1% hydrogen peroxide for 15 min to block endogenous peroxidase. Sections were then incubated overnight at 4°C with polyclonal antibodies against iNOS (1:1000; Santa Cruz Biotechnology, Inc., Santa Cruz, CA) and COX-2 (1:400; Santa Cruz Biotechnology, Inc.). After incubation with biotinylated rabbit anti-mouse and anti-goat antibodies, respectively, followed by incubation with streptavidin-peroxidase complex using ABC kit (Amersham Biosciences UK Ltd., Little Chalfont, Buckinghamshire, UK), the reaction products were detected by 0.03% dianisobenzidine and H2O2 in 0.05 M Tris-HCl buffer (pH 7.6). The sections were washed in phosphate-buffered saline three times between each step, the 3,3-diaminobenzidine tetrahydrochloride containing 0.05% hydrogen peroxide was applied for 3 min, the sections were rinsed with tap water, and then counterstained with hematoxylin. To ensure the specificity of the immuno-
histrochemical staining, the sections were processed without primary antibody.

RNA Extraction and Semiquantitative RT-PCR. The animals were given 3 mg/kg E. coli LPS i.v., and they were killed at 6 h later. The stomachs were quickly removed, frozen in liquid nitrogen, and stored at −80°C until needed. Stomach tissue samples were pooled from five rats for extraction of total RNA, which were prepared by a single-step acid phenol-chloroform extraction procedure, by using ISOGEN (Nippon Gene, Tokyo, Japan); and the concentration of RNA was adjusted to 1 μl/μl with RNase-free distilled water. Semiquantitative RT-PCR was performed as follows: first-strand cDNA was synthesized by using Takara Best RT-PCR kit (Takara, Kyoto, Japan) at 65°C for 1 min, 30°C for 5 min, 65°C for 5 min, and 98°C for 5 min by using a thermal cycler. PCR amplification was performed by the hot starting method, using Takara Best RT-PCR (Takara). The sequences of primers used in this study were designed according to the published study (Devaux et al., 2001). The sequences of sense and antisense primers for the rat COX-2 were 5'-TTCAAAGAAGTTCTGGAAAGGT-3' and 5'-GATCATGTCCATCCGGTCTCC-3', respectively, giving rise to 304-bp PCR product. Likewise, the sequences of sense and antisense primers for the rat iNOS were 5'-GATCAATACCTGAGCCCG-3' and 5'-GCCCTTTTTTTGCTCATAGG-3', respectively, giving rise to 578-bp PCR product. In addition, for the rat β-actin, a constitutively expressed gene, the sequences were 5'-GGGACCTCGAGGAGGAGATGG-3' for sense primer and 5'-GCACCGTGTTGGCGTAG-3' for anti-sense primer, giving rise to a 232-bp PCR product. After initial denaturation at 95°C for 10 min, cDNA of COX-2, iNOS, and β-actin were amplified at 20 to 40 cycles (five-cycle interval) of amplifications at 95°C for 60 s; 52, 60, and 65°C, respectively, for 30 s; and 72°C for 60 s by using a thermal cycler. PCR products in each cycle were electrophoresed on 2% agarose gel containing 0.1% ethidium bromide. Detectable fluorescent bands were visualized by an ultraviolet transilluminator, and the area was measured by using NIH Image software. The signals for examined mRNAs were 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. The expression of iNOS, COX-1, COX-2, and β-actin proteins was examined by Western blotting. Gastric specimens were taken from the rats and proteins were partially purified according to the method of Gierse et al. (1995). In brief, the specimens were homogenized in 25 mM Tris-HCl (pH 8.0) buffer containing 250 mM sucrose, followed by centrifugation at 10,000g for 20 min. The pellet was resuspended in a 25 mM Tris-HCl (pH 8.0) buffer containing 1 M (3-cholamidopropyl) dimethylammonio-1-propanesulfonate (CHAPS), and the mixture was gently stirred for 2 h at 4°C. The supernatant was recovered after centrifugation at 30,000g for 30 min and applied onto a DEAE-Sepharose CL-4B column (Amersham Biosciences UK, Ltd.) that had been equilibrated with a 25 mM Tris-HCl (pH 8.0) buffer containing 0.5% CHAPS, 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 carried out with 200 mM NaCl. After an aliquot (30 μg) of the eluted proteins had been subjected to SDS-polyacrylamide gel electrophoresis, the separated proteins were electrophoretically transferred onto Hybond-P membranes (Amersham Biosciences UK, Ltd.). The membranes were incubated with the primary polyclonal antibodies (Santa Cruz Biotechnology, Inc.) against iNOS, COX-1, COX-2, and the primary monoclonal antibody (Sigma-Aldrich) against β-actin protein overnight at 4°C after nonspecific binding sites had been blocked with nonfat milk. The excess primary antibody was removed by washing in buffer three times for 10 min. Then, the membranes were incubated with the horseradish peroxidase-conjugated secondary IgG antibody at a dilution of 1:1000 in Tris-buffered saline/Tween 20 (150 mM NaCl, 20 mM Tris-HCl, pH 7.5, and 0.05% Triton X-100) for 1 h. Subsequently, the membranes were washed three times at 20 min each with Tris-buffered saline/Tween 20. The proteins were detected on X-ray films (Fuji Film, Tokyo, Japan) with an enhanced chemiluminescence kit (Amersham Biosciences UK, Ltd.). The autoradiograph was then assessed semiquantitatively utilizing computer-assisted densitometry. Comparison between different groups was made by determination of the examined protein/β-actin protein ratio of the immunoreactive area by densitometry.

Myeloperoxidase Activity. MPO activity was determined by a modification of the method of Grisham et al. (1986). Hundred microliters of mucosal homogenates was centrifuged at 20,000g for 15 min at 4°C to form the insoluble cellular debris into pellets, which were then rehomogenized in an equivalent volume of 0.05 M potassium phosphate buffer (pH 5.4), containing 0.5% hexadecyltrimethylammonium bromide. The samples were centrifuged at 20,000g for 15 min, and the supernatant was saved. MPO activity was assessed by measuring the H2O2-dependent oxidation of 3,3',5,5'-tetramethylbenzidine. One unit of enzyme activity was defined as the amount of MPO present that caused a change in absorbance of 1.0/min at 655 nm at 25°C.

Statistics. Data are expressed as the mean ± S.D. of the values from five rats in each group. Statistical analyses were performed using a one-way analysis of variance followed by the Dunnett’s multiple comparison test. Values that had been associated with probability (p value) of <0.05 were considered significant.

Results

In Vivo NO Level in Gastric Mucosa after LPS Administration. NO produced in the gastric mucosa of rats was measured at 0, 2, 4, 6, 8, and 12 h after LPS administration. The NO levels in the unit of nanomoles per gram of tissue per 30 min (control, 0.35 ± 0.16, n = 5) increased

![Fig. 1](image-url)
gradually after administration, reached a maximum (13.3 ± 3.3, n = 5) at 6 h and then decreased thereafter (Fig. 1).

The increase in the NO level in the unit of nanomoles per gram of tissue per 30 min at 6 h after LPS injection was significantly suppressed (4.0 ± 0.4, n = 5) by preadministration of a selective iNOS inhibitor, 1400W, and also by that of a nonselective COX inhibitor, indomethacin, and a selective COX-2 inhibitor, NS-398 (Fig. 2). As shown in Fig. 2, pretreatment of COX inhibitors suppressed the NO level in the unit of nanomoles per gram of tissue per 30 min dose dependently (indomethacin: 10 mg/kg, 1.97 ± 0.62; 5 mg/kg, 4.9 ± 0.8; 1 mg/kg, 9.16 ± 1.98; NS-398: 10 mg/kg, 3.36 ± 1.03; 5 mg/kg, 6.7 ± 1.0; 1 mg/kg, 11.2 ± 0.81, n = 5).

Unless otherwise stated, the various measurements shown below were performed at 6 h after LPS administration, at that time the NO production was maximized as just described.

In Vivo PGE2 Level in Gastric Mucosa after LPS Administration. Administration of LPS caused a significant and time-dependent increase in the gastric mucosal concentration of PGE2 (control: 288 ± 16; 6 h, 806 ± 15 pg/g tissue, n = 5) (Fig. 3). Pretreatment of the rats with an iNOS inhibitor, 1400W, had no significant effect on the concentration of PGE2 (788 ± 26 pg/g tissue, n = 5) at 6 h after LPS administration, whereas that with COX inhibitors indomethacin and NS-398 inhibited the rise in the gastric mucosal concentration of PGE2. Compared with the selective COX-2 inhibitor NS-398, a nonselective COX inhibitor, indomethacin, more strongly suppressed the PGE2.

Gastric Mucosal iNOS and COX Expression after LPS Administration. Administration of LPS caused an increase in expression of iNOS in gastric mucosa compared with that of saline-treated control rats. The increase in iNOS
mRNA determined by semiquantitative RT-PCR (Fig. 4) correlated with an increase in iNOS protein measured by Western blot analysis (Fig. 5). The up-regulation was also associated with an induction of iNOS on the gastric epithelial cells as demonstrated by immunohistochemistry (Fig. 6). On the other hand, preadministration of neither iNOS nor COX inhibitors significantly modified iNOS mRNA and protein expression at 6 h after LPS administration (Figs. 4 and 5). Administration of LPS resulted in a time-dependent increase in COX-2 mRNA (Fig. 7) and protein (Fig. 8) expression, whereas it had no significant effect on the COX-1 protein (Fig. 9) expression. The up-regulation of COX-2 in the gastric mucosa after LPS administration was also evident on immunohistochemistry (Fig. 6). Alternatively, preadministration of neither iNOS nor COX inhibitors significantly modified COX-2 mRNA (Fig. 7) and protein (Fig. 8) expression at 6 h after LPS administration.

**MPO Activity.** MPO activity, an index of tissue-associated neutrophil accumulation, was assayed in gastric mucosa of rats treated with saline and LPS. No significant difference was observed in the MPO activity between the saline controls (3.747 ± 0.629 mU/mg protein, n = 5) and the rats at 6 h after LPS treatment (5.088 ± 0.823 mU/mg protein, n = 5).

**Discussion**

In the present study, in vivo cross talk between products from iNOS and COX in the rat gastric mucosa during endotoxemia was examined by evaluating the effects of iNOS or COX inhibitors on levels of NO, PGE2, and protein and mRNA of iNOS and COXs. In vivo NO production in the gastric mucosa was determined directly, by using an EPR NO trapping technique. We obtained following findings: 1) the administration of *E. coli* LPS caused a time-dependent increase in the levels of NO and PGE2 in the gastric mucosa and enhanced the expression of iNOS and COX-2 protein/mRNA without significant effect on MPO activity; 2) relatively specific iNOS inhibitor 1400W suppressed the increase in NO level of the gastric mucosa after LPS administration, but it did not have any effect on the increase in gastric mucosal PGE2 and expression of COX-1 and COX-2; and 3) both nonspecific COX inhibitor indomethacin and COX-2-specific inhibitor NS-398 inhibited the increase in gastric...
mucosal NO and PGE2 after LPS administration without any effect on the enhancement of expression of iNOS and COX; and the inhibitory effect of indomethacin on NO and PGE2 production was greater than that of NS-398.

The cross talk between NOS and COX pathway may be divided into two interactions that include NOS-derived NO with COX activity and COX-derived prostaglandins with NOS activity.

On the interaction of NO with COX activity, contradictory results have been reported with respect to whether NO enhances, inhibits, or has little effect on the COX activity (Goodwin et al., 1999; Coffey et al., 2001, and references therein). A variety of chemical reactivities of the NO radical would affect both conformation and activity of COX enzyme. NO can attack COX enzyme directly through the coordination to heme iron in the prosthetic group of the enzyme or the reaction with tyrosyl radical located in the active site (Salvemini et al., 1993; Gunther et al., 1997). In addition, NO influences the supply of COX substrate (Ma et al., 1996) and also COX-2 gene transcription (Dela Torre et al., 1997; Schmedtje et al., 1997). These in vitro experiments suggest that NO has the ability to lead the COX enzyme to two opposed states; activation or inactivation, depending on cell types used or experimental conditions.

Several studies performed in vivo are also controversial with respect to the interaction of NO with COX activity (Goodwin et al., 1999; Coffey et al., 2001, and references therein). A variety of chemical reactivities of the NO radical would affect both conformation and activity of COX enzyme. NO can attack COX enzyme directly through the coordination to heme iron in the prosthetic group of the enzyme or the reaction with tyrosyl radical located in the active site (Salvemini et al., 1993; Gunther et al., 1997). In addition, NO influences the supply of COX substrate (Ma et al., 1996) and also COX-2 gene transcription (Dela Torre et al., 1997; Schmedtje et al., 1997). These in vitro experiments suggest that NO has the ability to lead the COX enzyme to two opposed states; activation or inactivation, depending on cell types used or experimental conditions.

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These studies showed that the COX enzyme system widely contributes to iNOS gene induction and resultant NO production. In this study, performed in vivo, we showed that both nonselective and selective COX inhibitors, indomethacin and NS-398, respectively, suppressed the up-regulation in the gastric mucosal NO and PGE2 production that had been caused by systemic administration of LPS with their dose-dependent manners, although both inhibitors exerted neither reduction on iNOS nor COX-2 at their protein and mRNA levels. These results were essentially consistent with those observed in the cerebral tissues of restraint-stressed rat pretreated with NS-398 (Madrigal et al., 2003). Both indomethacin and NS-398 had been confirmed to have no direct inhibitory effect on enzymatic activity of iNOS in a cell free system (Posadas et al., 2000). Together, these findings suggest that COX-2 activity may be closely related to the functional activation of iNOS but not to the expression of iNOS protein and mRNA in the gastric mucosa of LPS-treated rats.

The production of NO derived from iNOS is dependent on the intracellular availability of either 1) cosubstrates for NO generation: L-arginine, NADPH, and oxygen; or 2) cofactors cooperating with the enzyme: tetrahydrobiopterin (H₄B), heme, flavin mononucleotide, and flavin adenine dinucleotide. These factors may play critical roles in NO production from iNOS, especially in vivo conditions, even though the enzyme expression is sufficient to produce NO in the gastric mucosa. On the other hand, two catalytic steps of COX-2, cyclooxygenase and peroxidase, are associated with the production of not only prostanoids but also reactive oxygen species (Vane et al., 1998). The peroxidase action of COX-2 may affect intracellular oxygen status and effect on the NO production derived from iNOS (Madrigal et al., 2003). In addition, hydrogen peroxide, one of the reactive oxygen species, is known to stimulate H₄B synthesis in vascular endothelial cells (Shimizu et al., 2003). Moreover, PGE2 may also play important roles in functional activation of iNOS enzyme through its receptor-regulated signaling mediated by a cAMP (Bulut et al., 1993; Chen et al., 1999). PGE2 has been shown to increase intracellular cAMP in gastric mucosal cells (Hiraishi et al., 1986). The cAMP is known to participate in functional activation of iNOS enzyme through 1) accelerating a transmembrane intake of L-arginine from the outside, and 2) suppressing intracellular metabolic conversion to L-citrulline in the cells (Ferro et al., 1999). Another way of the contribution of cAMP to iNOS activity is achieved by the induction of GTP cyclohydrolase I, a rate-limiting enzyme in H₄B biosynthesis (Pluss et al., 1996). These sug-
gest that COX-2 enzyme activity and/or its products, such as PGE2, may be closely implicated in functional activation of iNOS enzyme through regulating its cosubstrates and cofactors in addition to the expression of iNOS mRNA/protein. Alternatively, the post-translational modification, including protein stabilization, dimerization, phosphorylation, and subcellular localization, might explain the discrepancy between effects of PGE2 on NO production and iNOS protein/mRNA level. Consequently, these possibilities might lead to the discrepancy between the intracellular effects of COX activity on NO production and iNOS protein/mRNA expression. Regardless of the precise mechanisms, this in vivo study demonstrates that endogenous COX activity can modulate LPS-stimulated iNOS activity in the post-translational way. However, we analyzed only the production of PGE2 as the representative of COX activity, thus it is difficult to rule out the possibility that the NO production was influenced not only by PGE2 but also by another COX products, such as thromboxane A2 or prostacyclin. Additional study will be required to clarify the mechanisms of the post-translational modification of COX activity on NO production and, moreover, the regulatory mechanism of NO production by PGE2. The possible stimulatory role played by COX activity in NO production, in response to intracellular pathogens, is interesting in the light of a possible pharmacological regulation of the beneficial or detrimental effects of NO.

In summary, our data show that PGE2 in the LPS-treated rat gastric mucosa increases the release of NO after activation of iNOS, although NO produced by iNOS does not stimulate the release of PGE2 by COXs in the rat gastric mucosa. During the pathogenesis of endotoxin-induced gastric injury, COX activity may be an important factor of NO production, including a cofactor and costimulator of iNOS activity. The effect of COX activity on iNOS pathway may be important in fine-tuning and regulation of gastric mucosal integrity in inflammatory states.

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References


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